BLA Clinical Review Memorandum

Application Type	Complete Response (CR) to Original Application
STN	125428
CBER Received Date	8 February 2017
PDUFA Goal Date	9 November 2017
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Alexandra Worobec, M.D. (Immunogenicity) Darcie Everett, M.D., M.P.H. (Safety)
Review Completion Date / Stamped Date	9 November 2017
Supervisory Concurrence	Meghan Ferris, M.D., M.P.H.
	Andrea N. Hulse, M.D.
Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	Heplisav-B
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5 mL dose contains 20 mcg of recombinant yeast cell-derived hepatitis B virus surface antigen (HBsAg) and 3000 mcg Dynavax's proprietary adjuvant, 1018
Dosage Form(s) and Route(s) of Administration	Solution for Intramuscular Injection
Dosing Regimen	Two 0.5 mL doses administered four weeks apart
Indication(s) and Intended Population(s)	Active immunization against infection caused by all known subtypes of hepatitis B virus in adults age 18 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
ADAE	Analysis data model adverse event analysis dataset for CDISC
ADCM	Analysis data model concomitant medication analysis dataset for CDISC
ADMH	Analysis data model medical history analysis dataset for CDISC
ADSL	Analysis data model subject level analysis dataset for CDISC
AESI	adverse event of special interest
AMI	acute myocardial infarction
ANCA	anti-neutrophil cytoplasmic antibody
BIMO	Bioresearch Monitoring Program
BLA	Biologics License Application
BMI	body mass index
CAD	coronary artery disease
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CMC	Chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
CpG	cytosine phosphoguanine
CR	complete response
CRF	case report form
CSR	clinical study report
CTA	computed tomography angiography
CV	cardiovascular
dL	deciliter
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPA	granulomatosis with polyangiitis
GMC	geometric mean concentration
HbA1c	hemoglobin A1c
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
hr	hour
Ig	immunoglobulin
IM	intramuscular
IND	Investigational New Drug application
IR	information request
L	liter
LCPP	lot consistency per protocol
LMP	last menstrual period
LV	left ventricular
mcg	micrograms
MedDRA	Medical Dictionary for Regulatory Activities

MI	myocardial infarction
mITT	modified intent-to-treat
mIU	milli-international units
mL	milliliter
mM	millimole
ODN	oligodeoxynucleotide
PP	per protocol
PREA	Pediatric Research Equity Act
PT	preferred term rHBsAg recombinant hepatitis B surface antigen
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEAC	Safety Evaluation and Adjudication Committee
SPR	seroprotection rate
STN	submission tracking number
THS	Tolosa-Hunt Syndrome
TLR	toll-like receptor
TPO	thyroid peroxidase
TSH	thyroid stimulating hormone
TSI	thyroid stimulating immunoglobulin
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee
µIU	micro-international units

1. Executive Summary

Dynavax, the Applicant, submitted Biologics License Application (BLA) STN 125428/0 to the Center for Biologics Evaluation and Research (CBER), of the Food and Drug Administration (FDA) on 26 April 2012 intended to support licensure of a recombinant hepatitis B virus vaccine adjuvanted with a novel cytosine phosphoguanine enriched oligodeoxynucleotide phosphorothioate sequence (1018 adjuvant) with the proposed trade name Heplisav-B. The proposed indication and use at the time was for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age.

Because of the novel nature of the adjuvant, a Vaccines and Related Products Advisory Committee (VRBPAC) was held to discuss the product's immunogenicity and safety on 15 November 2012. The committee voiced concerns about the size of the safety database submitted in support of licensure and recommended that additional safety information be obtained in a larger population.

On 22 February 2013, CBER issued a Complete Response (CR) letter. In addition to a number of non-clinical concerns, three clinical items precluded approval at that time: 1) the inadequate size of the safety database; 2) the need for additional information regarding a number of specific adverse events; and 3) the need for information regarding a case of possible Tolosa-Hunt syndrome (THS) in a Heplisav-B recipient in study DV2-HBV-16. THS is a rare syndrome with an estimated annual incidence of one case per million per year[1] characterized by painful ophthalmoplegia (weakness of the eye muscles) caused by an idiopathic granulomatous inflammation of the cavernous sinus. Additionally, the Bioresearch Monitoring (BIMO) reviewer identified concerns which

precluded approval at that time and were based on inspection findings from Study DV2-HBV-16.

Following the CR letter, the Applicant conducted an additional study to increase the size of the total safety database, study DV2-HBV-23. A secondary, descriptive endpoint of this study was the proportion of subjects diagnosed with granulomatosis with polyangiitis (GPA) and Tolosa-Hunt syndrome (THS). The Applicant included this secondary endpoint because two Heplisav-B recipients were diagnosed with these inflammatory vasculitic conditions in previous studies: one subject with GPA (formerly "Wegener's granulomatosis" and so diagnosed at the time the study was conducted) in study DV2-HBV-10 and the possible case of Tolosa-Hunt syndrome in study DV2-HBV-16 noted above.

CBER solicited outside consultations from several experts regarding the possible diagnosis of Tolosa-Hunt Syndrome, incorporating additional information submitted by the Applicant in response to CBER's request in the February 2013 CR letter. All four consultants assessed the event as Tolosa-Hunt syndrome, each of them noting the subject's response to steroids and reasonable exclusion of alternate etiologies. None of the consultants endorsed a definitive causal association between the vaccine and the adverse event.

The Applicant's complete response to the February 2013 CR letter was received on 16 March 2016, including the Clinical Study Report (CSR) and supporting documents from the additional safety study, DV2-HBV-23, and information intended to address the other two clinical CR letter items. In this submission, the Applicant revised the proposed usage to remove the upper age restriction of 70 years, but did not provide a rationale or additional data to support the revision.

The March 2016 submission also included revised CSRs for studies DV2-HBV-10 and DV2-HBV-16. The Applicant determined these revisions were necessary to correct errors in the DV2-HBV-10 and DV2-HBV-16 CSRs submitted previously to the BLA in 2012. The Applicant stated that it detected these errors during audits performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA. However, the Applicant did not include datasets for studies DV2-HBV-10 and -16 to support the revised CSRs. This deficiency and the subsequent submission of revised datasets for DV2-HBV-10 and -16 resulted in a Major Amendment.

The revisions to the CSRs for DV2-HBV-10 and -16 primarily concerned subjects erroneously included or excluded from the per protocol (PP) immunogenicity populations of each study. The safety populations for neither study changed as a result of the audit. Thus, CBER's review of the revised CSRs for studies DV2-HBV-10 and -16 focused exclusively on the revised immunogenicity data.

CBER identified additional subject accounting discrepancies in the revised CSRs for DV2-HBV-10 and -16 and the revised datasets for DV2-HBV-10 and -16 that had not been identified as part of the Applicant's revised submission. Despite a number of communications with the Applicant during the second review cycle, persistent inconsistencies in the responses to information requested contributed to CBER issuing a second CR letter on 10 November 2016.

The Applicant's complete response to the November 2016 CR letter was received on 8 February 2017, beginning the third (and current) review cycle. With the submission of this additional information, the Applicant satisfactorily addressed outstanding concerns regarding subject accounting for the PP populations of studies DV2-HBV-10 and -16. Using the revised per protocol populations, the primary immunogenicity endpoints for both studies DV2-HBV-10 and -16 were similar to those in the respective original CSR, with only minor numerical differences noted in SPRs and 95% confidence intervals for each respective comparison. Thus, these studies demonstrated non-inferiority of Heplisav-B with the active comparator vaccine, Engerix-B, thereby showing effectiveness of Heplisav-B against hepatitis B virus infection in adults 18-70 years of age. CBER reviewed immunogenicity data from DV-HBV-23 primarily to confirm similarity with the original and revised immunogenicity results of studies DV2-HBV-10 and -16. Non-inferiority of the immune response in adults 18-70 years old, regardless of diabetic status, was a secondary endpoint. Vaccine effectiveness in adults 18-70 years old, which CBER considered established by DV2-HBV-10 and -16, was also supported by DV2-HBV-23. The primary immunogenicity endpoint in study DV2-HBV-23 was a comparison of the SPR between Heplisav-B and Engerix-B at Week 28 in type 2 diabetic subjects. Additional subgroup analyses for immunogenicity were performed based on sex, age, race, body mass index (BMI), and smoking status. CBER viewed DV2-HBV-23 as a safety study conducted in response to item #1 in the February 2013 CR letter, which cited a safety database of inadequate size. Neither the CBER nor the VRBPAC cited a deficiency in the size of the immunogenicity database. Therefore, CBER neither requested nor considered the additional immunogenicity data generated in DV2-HBV-23 necessary to render a decision on the originally proposed indication.

Because of study DV2-HBV-23's importance in the safety assessment of Heplisav-B, BIMO inspections of select study DV2-HBV-23 sites were performed during the second review cycle and identified data inconsistencies in a subset of randomly selected subjects incorrectly labeled as PP subjects at one site (site 122/222). However, the BIMO reviewer considered the Applicant's February 2017 complete response to have addressed these concerns.

In study DV2-HBV-23, safety outcomes of medically attended adverse events (MAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) were monitored through Week 56, one-year following the second and final dose of Heplisav-B. Solicited adverse events and unsolicited adverse events that were not medically attended were not collected and are not addressed directly in this review. A laboratory sub-study was also conducted to evaluate renal function and factors pre-disposing to thrombophilia following vaccination with Heplisav-B.

The Safety Population in DV2-HBV-23 consisted of 8368 subjects, 5587 who received at least one dose of Heplisav-B and 2781 who received at least one dose of Engerix-B. Baseline demographics were balanced between the two treatment groups, including medical conditions and cardiac risk factors (prior diagnosis of cardiac ischemic disease: 3.8% Heplisav-B, 3.6% Engerix-B; type 2 diabetes mellitus: 13.6% Heplisav-B, 13.7% Engerix-B; smoking: 33% Heplisav-B, 33% Engerix-B; obesity: 49% Heplisav-B, 46% Engerix-B). Subjects in DV2-HBV-23 reported more baseline medical conditions and risk factors for coronary artery disease than those enrolled in DV2-HBV-10 and -16 (for example, prior diagnosis of cardiac ischemic disease: 3.7% DV2-HBV-23, 2.7% DV2-HBV-16, 0.6% DV2-HBV-10; type 2 diabetes mellitus: 13.7% DV2-HBV-23, 7.8% DV2-

HBV-16, 2.2% DV2-HBV-10; hypertension: 36% DV2-HBV-23, 29% DV2-HBV-16, 39% DV2-HBV-10, smoking: 33% DV2-HBV-23, 22% DV2-HBV-16, 36% DV2-HBV-10).

Overall, the rates of all MAEs (46.0% Heplisav-B, 46.2% Engerix-B) and non-fatal SAEs (5.8% Heplisav-B, 5.1% Engerix-B) reported in the 56-week study period were similar between the Heplisav-B and Engerix-B groups. Although overall rates were similar between treatment groups, imbalances in some preferred terms were noted.

Regarding MAEs three preferred terms were reported in at least 0.5% of either treatment group and at least twice the frequency in one treatment group compared to the other: herpes zoster (0.7% Heplisav-B, 0.3% Engerix-B), tooth infection (0.3% Heplisav-B, 0.6% Engerix-B recipients), and exostosis (0.1% of Heplisav-B, 0.5% of Engerix-B recipients).

Regarding SAEs, 14 subjects in the Heplisav-B group (0.25%) and one subject in the Engerix-B group (0.04%) reported a treatment-emergent acute myocardial infarction, making this preferred term the highest relative risk (RR) for subjects in the Heplisav-B group compared to the Engerix-B group (6.97, 95% Koopmans score confidence interval 1.17, 41.44). When additional SAEs that may represent myocardial infarctions mapped to different preferred terms were considered, based upon the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for myocardial infarction (MI) (includes the preferred terms acute myocardial infarction, myocardial infarction, coronary artery occlusion, acute coronary syndrome, and angina unstable), 19 Heplisav-B subjects (0.3%) and three Engerix-B subjects (0.1%) reported an SAE of MI. The RR of MI, based on the SMQ was 3.15 (95% Wald CI 0.93, 10.64; 95% Koopman score CI 1.00, 9.98). All subjects reporting an MI had at least one cardiovascular risk factor. Cardiovascular risk factors were similar between trial arms at baseline. More subjects in the Heplisav-B group reported MIs at approximately 2 -3 months following any dose of study vaccine and in the later six months of the study follow-up period compared to the Engerix-B group. A difference between trial arms in MI was not observed in prior studies; however, as noted above, subjects enrolled in DV2-HBV-23 had more cardiovascular risk factors than those enrolled in prior studies. Regarding other SAEs, a numerical imbalance in pulmonary embolism had been noted at the time of the 2012 BLA submission; however, no differences between study groups were noted in pulmonary embolism or other venous thromboembolic events (0.21% Heplisav-B, 0.25% Engerix-B) in study DV2-HBV-23.

An imbalance between treatment groups was also observed in deaths. After excluding deaths that were clearly due to illicit drug overdose or injury, an imbalance remained (0.29% Heplisav-B, 0.14% Engerix-B). No deaths were assessed as having a known relationship to study vaccine by investigators or the reviewer. No clear imbalance in a particular cause of death was identified.

Further analyses regarding the imbalance in MIs, as well as other information, were requested from the Applicant in an information request (IR) 9 September 2016. The Applicant submitted responses 26 September - 11 October 2016. The need for a full review of these responses and evaluation of the safety of Heplisav-B in the context of the above noted imbalances, contributed to CBER issuing a second CR on 10 November 2016 referenced previously.

In response to questions from CBER concerning the findings, the Applicant submitted a major adverse cardiovascular events (MACE) analysis in response to the 9 September 2016 IR, which was reviewed in the third (and current) review cycle. This analysis was based on a post-hoc, blinded adjudication of possible events of cardiac death, myocardial infarction, and stroke occurring in the three pivotal studies performed by the Applicant's external expert consultants. In DV2-HBV-23, 47 events reported in 44 subjects were reviewed to determine if they were a MACE. In DV2-HBV-23, 28 subjects in the Heplisav-B group (0.5%) and 6 subjects in the Engerix-B group (0.22%) reported an event adjudicated as a MACE, including 14 subjects in the Heplisav-B group (0.25%) and 1 subject in the Engerix-B group (0.04%) with adjudicated MI. Based upon adjudicated events, the relative risk of non-fatal MI and the composite three-point MACE outcome in study DV2-HBV-23 was 6.97 (95% Koopman score CI 1.17, 41.44) and 2.32 (95% Koopman score CI 0.99, 5.46), respectively. Based on the adjudications, a similar proportion of subjects in both treatment groups experienced a cardiovascular death, but more subjects in the Heplisav-B group were adjudicated as having an unknown cause of death [7 (0.13%) Heplisav-B subjects vs. 0 Engerix-B subjects].

CBER obtained three cardiology consultations (appended to this document) for input in evaluating these analyses. All three consultants agreed that the Applicant had performed a reasonable post-hoc analysis of cardiac events following Heplisav-B. Two consultants advised that further evaluation with studies prospectively designed to assess cardiac risk are necessary to determine whether or not there is an increased risk of cardiovascular events following Heplisav-B. One consultant opined that the data suggest a "low likelihood that there is a real safety signal here, and [a] low absolute risk…" and indicated that post-marketing passive surveillance would be appropriate to monitor risk. Upon review of the additional analyses and consultations, the clinical reviewer judges the imbalance in MI observed in this large randomized, controlled, safety trial conducted in a study population with cardiovascular risk factors to represent a safety signal of increased risk for myocardial infarction in association with receipt of Heplisav-B.

With regard to autoimmune disease, due to a theoretical concern that novel adjuvants could be associated with autoimmunity and the previously reported events of two rare granulomatous vasculitides in studies DV2-HBV-10 and DV2-HBV-16, any potential AESIs in study DV2-HBV-23 were referred to a Safety Evaluation and Adjudication Committee (SEAC) for assessment of accurate diagnosis, timing of onset, and relationship to study vaccine. AESIs were identified by investigators using a pre-specified list of conditions that CBER considers potentially immune-mediated. A similar number of subjects in each treatment group reported MAEs that were suspected to be potential AESIs by investigators and were referred to the SEAC for evaluation (0.7% Heplisav-B, 0.8% Engerix-B). The SEAC adjudicated four events as new-onset autoimmune events (one subject each with alopecia areata, hypothyroidism [Hashimoto's thyroiditis], polymyalgia rheumatica, and ulcerative colitis). They determined that none of these events were related to vaccination and that one event (hypothyroidism) was due to an alternative cause (papillary thyroid carcinoma). In addition, several events, for which the SEAC agreed with the diagnosis but determined the event was not autoimmune, are included on the AESI list and are considered by the CBER to be potentially immune-mediated (for example, cranial nerve palsies, in particular Bell's palsy). There were nine subjects in the Heplisav-B group (0.2%) who reported these immune-mediated events (Bell's palsy in five subjects, alopecia areata, hypothyroidism, polymyalgia rheumatica, and ulcerative colitis). One subject in the

Engerix-B group (0.03%) reported a new-onset AESI (Bell's palsy). In addition, there was one subject in the Heplisav-B group who reported granulomatous dermatitis, a potentially immune-mediated skin condition that is often concurrent with systemic immune-mediated disease, following Heplisav-B administration. The dermatopathologist recommended an evaluation for sarcoidosis, which was not completed. The SEAC adjudicated this event as not autoimmune.

The laboratory sub-study was conducted in 309 subjects enrolled at two sites. Review of chemistry, hematology, and urinalysis assessments conducted at time points through the 56-week study period did not identify notable differences between study groups. Slightly more subjects in the Heplisav-B group had elevated Week 8 anti-beta2 glycoprotein 1 IgM levels. The clinical significance of one abnormal antiphospholipid antibody level is unclear.

The integrated analysis of safety conducted by CBER focused on SAEs and AESIs, as these safety outcomes were collected in DV2-HBV-23 and in previous trials. In the 10 November 2016 CR letter, CBER requested the Applicant submit an addendum to their integrated summary of safety, basing the analysis on three integrated safety populations. These populations differed from the populations presented by the Applicant because of concerns integrating studies with different lengths of follow-up, different safety endpoints (adverse events versus MAEs), and employing different formulations of the vaccine. No new safety issues were identified in the integrated analysis that were not previously identified. The response to the 9 September IR, included a MACE analysis of the data from the three pivotal trials, DV2-HBV-10, -16, and -23. As discussed above, adjudicated events of myocardial infarction occurred at a greater frequency in Heplisav-B recipients compared to the active comparator in study DV2-HBV-23. The Applicant reported the imbalances noted in study DV2-HBV-23 were diminished in magnitude when the two other pivotal trials were considered. However, pooling of the pivotal trials in order to assess cardiovascular risk in particular, adds a disproportionate number of lower risk subjects to the Heplisav-B group given the known differences in baseline cardiovascular risk of the study populations and the different randomization ratios of the trials. For these reasons, while CBER presents overall SAEs in the integrated populations, cardiovascular risk is presented separately for each study.

In the two pivotal studies that utilized review of potential AESIs by an expert panel, both demonstrated that a small number of new-onset AESIs were reported almost exclusively in the Heplisav-B groups. In DV2-HBV-16 and -23, the Applicant identified 15 subjects who received Heplisav-B (0.20%) and one subject who received Engerix-B (0.03%) and reported new-onset immune-mediated events. In addition to the nine immune-mediated events listed above that occurred in DV2-HBV-23, a total of six immune-mediated events occurred in DV2-HBV-16 as follows in one subject each except when noted: hypothyroidism (n = 2), THS, Bell's palsy, erythema nodosum, and vitiligo in the Heplisav-B group. No immune-mediated events were reported in DV2-HBV-16 in the Engerix-B group. Six Heplisav-B recipients (0.08%) and one Engerix-B recipient (0.03%) reported Bell's palsy. When studies that did not prospectively collect AESIs are also considered, the difference in frequency of Bell's palsy is more balanced (0.07% Heplisav-B, 0.05% Engerix-B). In the pivotal trials, including studies that prospectively and retrospectively identified AESIs, three potentially systemic granulomatous diseases were identified: GPA was reported in DV2-HBV-10, THS in DV2-HBV-16, and granulomatous dermatitis in DV2-HBV-23. Consultants assessed the first two diagnoses as pathologically distinct. However, given each of these disorders is very rare, the

likelihood of all three occurring by chance in a safety database of < 10,000 Heplisav-B recipients is very low.

In conclusion, two doses of Heplisav-B met pre-specified criteria demonstrating immunological non-inferiority as compared to the active comparator, Engerix-B, in healthy adults 18-70 years of age in three phase 3 clinical trials: DV2-HBV-10, -16, and -23. Additionally, two doses of Heplisav-B met pre-specified criteria demonstrating immunological non-inferiority as compared to the active comparator, Engerix-B, in subjects with type 2 diabetes in study DV2-HBV-23.

Regarding safety, in study DV2-HBV-23, clinically significant differences between treatment groups were observed in rates of myocardial infarction and in deaths. The differences between study groups in MI persisted when blinded adjudication of cardiovascular events was performed by the Applicant. Analysis showed that baseline cardiovascular risk factors were similar between study groups and thus, could not explain the differences between treatment groups. While these imbalances were not observed in studies other than DV2-HBV-23, this could be explained by the higher prevalence of cardiovascular risk factors in that study. Imbalances were also observed in overall AESIs, or potentially immune-mediated events, in DV2-HBV-16 and -23 (the studies that prospectively monitored for these events and utilized an expert committee to adjudicate them). Two distinct, rare, serious, inflammatory vasculitic conditions of granulomatous or presumed granulomatous pathology were reported following Heplisav-B in two subjects without pre-existing autoimmune disease. An additional event of granulomatous dermatitis was reported in DV2-HBV-23. For both the MIs and AESIs, numbers and rates of events are low. The lack of prospectively defined monitoring and evaluation of cardiac events also limits the interpretation of these observations. However, given the magnitude of the differences between study groups, particularly for MIs and adjudicated MIs, the clinical reviewer remains concerned that these events represent a true safety signal. Given that the vaccine is for prevention of Hepatitis B, a disease with consistently diminishing prevalence in the U.S. for which safe and effective U.S. licensed vaccines exist, in the judgement of the clinical reviewers the risk benefit profile of Heplisav-B is not favorable and approval is not recommended based on the available data.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary
In study DV2-HBV-23, subjects who received at least one vaccination had a mean age of 50.4 years. Randomization was stratified by age groups (18 – 39 and 40 – 70 years of age), but analysis of immunogenicity by 10 – 12 year subgroups was pre-specified. Approximately 5% of subjects were 18 – 29 years, 16% were 30 – 39 years, 23% were 40 – 49 years, 32% were 50 – 59 years and 25% were 60 – 70 years of age. As per CBER request, safety was also evaluated post-hoc in subjects younger than 65 and 65 years of age or older. Twelve percent of subjects were 65 - 70 years of age. Subjects vaccinated in the study were 50.6% male; 71.4% White, 25.8% Black, 1.1% Asian, 1.0% American Indian or Alaska Native; 90.9% not Hispanic, and 9.1% Hispanic. Enrollment of Whites (77% U.S.) was representative of the U.S. population. Relative to the U.S. population, Black/African Americans were over-represented (13% U.S.) and Asians were under-represented (5% U.S.) in DV2-HBV-23. The 2012 VRBPAC raised concern that Asians were also underrepresented in studies DV2-HBV-10 and -16. Hispanics were also under-represented (18% U.S.) based on 2016 census data[2].

Review of immunogenicity based on demographic characteristics (age, sex and race/ethnicity) for study DV2-HBV-23 showed similar findings for the seroprotective rate (SPR) response in subjects vaccinated with Heplisav-B, to those seen for the corresponding demographic subgroups in studies DV2-HBV-10 and -16. The most demonstrable difference in SPRs was seen by age. Younger subjects had higher SPRs than older subjects, though the SPRs were within an 8% difference between the youngest (18-29 years) and oldest age group (60+ years). The numerical differences in SPR rates by sex was negligible, as it was by race and ethnicity, though the majority of study subjects were white.

Following CBER's request in the 10 November 2016 CR letter, the Applicant provided a post-hoc summary of safety based upon demographic characteristics in study DV2-HBV-23. Differences between treatment groups in deaths and acute myocardial infarction were noted in the study as a whole, with more subjects in the Heplisav-B group reporting these events. Because of this and based on what was provided by the Applicant, rates of (unadjudicated) MIs and of deaths (including accidental deaths), as well as overall medically attended adverse events (MAEs) and overall serious adverse events (SAEs), by demographic subgroups are described below.

MAEs were reported at similar frequencies between treatment groups in subjects 18 – 40 (37% both groups), 40 and older (48% both groups), 18 – 64 (44% in Heplisav-B, 45% Engerix-B) and 65 years of age and older (63% Heplisav-B, 59% Engerix-B). The proportion of subjects reporting SAEs was slightly higher in the Engerix-B group in subjects 18 – 39 years of age (2.7% Heplisav-B, 3.6% Engerix-B), similar between treatment groups in subjects 40 and older (7.0% Heplisav-B, 5.8% Engerix-B), and 18 – 64 (5.5% Heplisav-B, 4.9% Engerix-B), and slightly higher in the Heplisav-B group in subjects 65 years of age and older (11.1% Heplisav-B, 8.3% Engerix-B). Unadjudicated events of myocardial infarction, identified using a standard query for preferred term, were reported by more subjects in the Heplisav-B group compared to the Engerix-B group for subjects 40 and older (0.4% Heplisav-B, 0.14% Engerix-B), 18 – 64 (0.3% Heplisav-B, 0.08% Engerix-B), and 65 years of age and older (0.9% Heplisav-B, 0.3% Engerix-B). One myocardial infarction was reported in one subject who was younger than 40 years of age (0.09%) in the Heplisav-B group and none in the Engerix-B group. Deaths were reported in more subjects in the Heplisav-B group compared to the Engerix-B group in subjects 40 years of age and older (0.5% Heplisav-B, 0.3% Engerix-B) and 18 – 64 (0.4% Heplisav-B, 0.2% Engerix-B) years of age.

No notable differences in safety between treatment groups were apparent by sex, with the exception of deaths in women, which occurred in nine women in the Heplisav-B group (0.3%) and one woman in the Engerix-B group (0.07%). Deaths due to causes other than injury or illicit drug overdose occurred in six women in the Heplisav-B group (0.2%) and no women in the Engerix-B group. As reported by investigators, three women died of cardiovascular causes (hypertensive heart disease, cardiac arrest, and cardiorespiratory arrest occurring 225 – 298 days after the last active dose), two women died of unknown causes (59 and 354 days after the last active dose), and one died of small cell lung cancer. As determined by the Applicant's post-hoc blinded adjudicators, two women died of cardiovascular causes (hypertensive heart disease at 225 days and death – cause unknown at 354 days after the last active dose) and three died of unknown causes (cardiac arrest, cardiorespiratory arrest, and death – cause unknown 59 – 298 days after the last active dose). As in the study population, deaths and

myocardial infarction in both sexes were reported at slightly higher frequencies in the Heplisav-B group.

No notable differences between treatment groups in overall MAEs or SAEs were identified by race for Whites and Black or African Americans, the two racial groups with significant numbers enrolled in study DV2-HBV-23. Differences were noted between treatment groups for the following races: Asians (N = 95, MAEs reported in 42% Heplisav-B recipients, 53% Engerix-B recipients), American Indian or Alaska Natives (N = 84, SAEs reported in 5% Heplisav-B recipients, 13% Engerix-B recipients), Native Hawaiian or Other Pacific Islander (N = 21, MAEs reported in 57% Heplisav-B recipients, 14% Engerix-B recipients), and Other Races (N = 34, MAEs reported in 48% Heplisav-B, 33% Engerix-B). It is difficult to draw conclusions based on race, particularly in subgroups with low enrollment. More deaths were reported in the Heplisav-B group (0.5%) compared to the Engerix-B group (0.1%) in Whites, but not in Black or African Americans (0.5% Heplisav-B, 0.6% Engerix-B). Myocardial infarction was reported at greater frequencies in the Heplisav-B group in Whites (0.4% Heplisav-B, 0.1% Engerix-B) and in Black or African Americans (0.2% Heplisav-B, 0.1% Engerix-B).

While MAEs were reported at similar frequencies in the two treatment groups by ethnicity, SAEs were reported at a greater frequency in the Heplisav-B group in Hispanic or Latino subjects (7.9% Heplisav-B, 3.3% Engerix-B). All deaths and all but one myocardial infarction were reported in Non-Hispanic or Latino subjects.

2. Clinical and Regulatory Background

Product: Heplisav-B (rHBsAg-1018 adjuvant)

- Recombinant Hepatitis B surface antigen (rHBsAg), subtype *adw*, produced in yeast cells (*Hansenula polymorpha*).
- Combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate adjuvant. The 1018 adjuvant used in Heplisav-B is a 22-mer oligonucleotide with the sequence:

  5’ TGA CTG TGA ACG TTC GAG ATG A 3’

Proposed Indication: For immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

Dosage and Administration: Each 0.5 mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 adjuvant. The dosing regimen is two 0.5 mL doses administered four weeks apart.

2.1 Disease or Health-Related Condition(s) Studied

Worldwide, more than 250 million persons are infected with Hepatitis B virus (HBV). Approximately 887,000 deaths worldwide were reported in 2015, mostly due to chronic hepatitis B, and resultant end-stage liver disease and/or hepatocellular carcinoma.[3]

In the U.S., universal childhood vaccination has been recommended since 1991. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.1 per 100,000 (2015). In the United States 850,000 persons are thought to be living with HBV, although other studies have estimated this number as high as 2.2 million. In 2015, the CDC reported 1,715 deaths in the U.S. noting hepatitis B as

an underlying cause, using reported U.S. death certificate data. Also in 2015, incidence of acute hepatitis B was highest for persons aged 30–39 years (2.6 cases/100,000 population) and approximately two-thirds of chronic hepatitis B cases are reported in persons 25–55 years of age. While CDC estimates the incidence of acute HBV infections in Asian/Pacific Islanders is low (0.35 per 100,000), unpublished surveillance data from CDC suggest that about one-half of chronic HBV infections were among Asian/Pacific Islanders. Forty-seven to 70% of U.S. residents with chronic HBV infection were born in other countries.[4]

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S. transmission is primarily sexual, followed by injection drug use. In 2015, 30% of persons with acute hepatitis B infection reported injection drug use.[4] Nosocomial transmission between patients and from patients to health care workers, including in the setting of hemodialysis (HD) and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens. The prevalence of HBV infection among hemodialysis patients was 1.2% in 2002.[5] In 2015, 0.2% of persons with acute hepatitis B infection reported receipt of dialysis or kidney transplant.[4]

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in infants, children, adolescents, and adults as a three-dose series to be administered on a 0-, 1-, and 6-month schedule. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Twinrix is licensed as a three-dose series, administered at months 0, 1, and 6. Additionally an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12.

These vaccines are highly effective, as shown in controlled clinical trials of efficacy against acute hepatitis B infection[6] and prospective observational studies,[7, 8] and elicit a SPR in approximately 95% of healthy adults. Long-term studies of immunocompetent adults and children indicate that immune memory remains intact for up to two decades and protects against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time.[8]

Breakthrough infections (detected by presence of anti-HBc antibodies or HBV DNA) have occurred in immunized people, but these infections typically are transient and asymptomatic.[9, 10] Chronic HBV infection in immunized individuals has been documented in dialysis patients whose anti-HBsAg antibody concentrations fell below 10 mIU/mL.[10] For adults on dialysis, formulations of Recombivax HB and Engerix-B containing 40 mcg HBsAg per dose (standard adult dose is 10 or 20 mcg of HBsAg, respectively) administered in a 3 or 4 dose series, respectively, are approved. In dialysis patients, the need for booster doses is assessed by annual antibody testing, and revaccination is recommended when anti-HBsAg levels decline below 10 mIU/mL.[9-11]

2.3 Safety and Efficacy of Pharmacologically Related Products
Currently, there are no approved vaccine products containing this novel 1018 adjuvant. Additionally, limited prior human experience exists for the 1018 adjuvant.

More clinical experience is available with other CpG oligonucleotides (ODNs), in particular CpG 7909 (ProMune, Coley Pharmaceuticals), a synthetic cytosine phosphoguanine oligonucleotide agonist of TLR9. CPG 7909 has been evaluated in numerous clinical trials, most commonly in the context of use in the cancer patient population. While these studies have been difficult to interpret due to the heterogeneous population of patients evaluated in clinical trials, to date no significant autoimmune signals have been reported.[12, 13] Autoantibody seroconversions have been reported in a small proportion of patients treated with CpG ODNs (≤ 10%), specifically anti-dsDNA and ANA, but without evidence of clinical disease.[12]

CpG 7909 has been administered with Engerix-B in a double-blind phase 1/2 study in 42 healthy subjects 18-35 years of age.[14] The most frequently reported adverse events were injection site reactions, flu-like symptoms and headache. Autoimmune adverse events were not reported. A second, similar study performed in thirty-eight HIV-infected individuals 18-55 years of age[15] failed to reveal any autoimmune adverse events, although transient elevations above normal range for anti-dsDNA were noted in two subjects who received Engerix-B plus CpG 7909 and in two subjects who received CpG 7909 alone. These subjects were ANA negative. A third study, a phase 1 double-blind study, evaluated CpG 7909 and Anthrax Vaccine Adsorbed (BioThrax) in 69 healthy subjects 18-45 years of age.[16] Safety monitoring was performed for six months after the last vaccination. No serious adverse events related to study agents were reported, and the combination was considered to be reasonably well tolerated. A follow-up phase 1 study of BioThrax plus CPG 7909 was conducted in 105 healthy adults 18-50 years of age.[17] The most common adverse events (AEs) in the BioThrax alone and BioThrax plus CpG 7909 groups assessed by investigators as related to vaccination were injection site reactions. No autoimmune events were observed in the study.

2.4 Previous Human Experience with the Product (Including Foreign Experience)
This product is not approved anywhere else in the world. A marketing authorization application was submitted to the European Medicines Agency (EMA) in 2012 intended to support an indication for immunization against infection caused by all known subtypes of HBV in adults 18 through 70 years of age and in patients with chronic kidney disease (CKD). In 2014, Dynavax officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application. According to the EMA website,[18]

> "The Committee considered that the way in which the study in patients with kidney disease had been carried out and documented was not satisfactory. This followed an inspection of some of the sites involved in the study, to ensure proper standards for medicines studies (Good Clinical Practice) had been followed. The nature of the findings from the inspection also raised questions about the other main studies. Therefore, there were serious uncertainties at that point about the reliability of the data submitted in support of the application. Furthermore, the number of patients in whom the safety of the medicine had been tested was insufficient to rule out an unacceptable level of risk for less common but serious side effects.

> Therefore, at the time of the withdrawal, the CHMP was of the opinion that the medicine could not have been approved based on the data presented by the company."

In its EMA withdrawal letter, available through the EMA website[18], Dynavax stated it could not provide the additional safety data required by the CHMP within the allowed timeframe.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

> 26 April 2012: Submission of BLA STN 125428/0
>
> 15 November 2012: Vaccines and Related Products Advisory Committee (VRBPAC) expressed concerns with the size of the safety database, as well as underrepresentation of Asian subjects enrolled in the trials.[19]
>
> 22 February 2013: Center for Biologics Evaluation and Research (CBER) issued a CR letter based on review of submissions to STN 125428/0, with the exception of amendments dated 29 December 2012, 16 January 2013, 1 February 2013, and 7 February 2013. In addition to a number of non-clinical concerns, clinical items precluding approval at that time included the inadequate size of the safety database, the need for additional information regarding a number of adverse events and a possible case of Tolosa-Hunt syndrome in one Heplisav-B recipient in study DV2-HBV-16. Two CR items were generated from the Bioresearch Monitoring (BIMO) reviewer as a result of inspection findings from study DV2-HBV-16.
>
> 16 March 2016: Applicant's complete response to the February 2013 CR letter received. In addition to the Clinical Study Report (CSR) and supporting documents from the required safety study, DV2-HBV-23, the submission included revised CSRs for studies DV2-HBV-10 and DV2-HBV-16. The Applicant determined these revisions were necessary due to errors it detected during audits performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA. However, the submission lacked datasets for studies DV2-HBV-10 and DV2-HBV-16 to support CBER's verification of the revised CSRs.
>
> 8 April 2016: Applicant submitted datasets for studies DV2-HBV-10 and DV2-HBV-16 at CBER's request, received on 11 April 2016.
>
> 18 April 2016: CBER notified the Applicant that the datasets constituted a Major Amendment because they contained a substantial amount of new data not previously submitted to, or reviewed by the Agency, thus adding an additional three months to the review clock. Therefore, the action due date was revised to 15 December 2016.
>
> 27 May 2016: Applicant responded to a CBER Information Request (IR) regarding revised immunogenicity data for studies DV2-HBV-10 and DV2-HBV-16 and included newly revised subject disposition datasets for these two studies, as well as a tabular summary of subjects whose disposition changed based on the audit.

12 July 2016: Applicant responded to a CBER IR again seeking clarity regarding subject disposition in studies DV2-HBV-10 and DV2-HBV-16 with tabular summaries and datasets.

3 August 2016: CBER discussed inconsistencies in the data submitted regarding subject disposition in studies DV2-HBV-10 and DV2-HBV-16 in a teleconference with the Applicant.

9 September 2016: CBER requested additional information to support assessment of safety in study DV2-HBV-23, as well as information needed to support evaluation of immunogenicity assessments and subject disposition for studies DV2-HBV-10 and DV2-HBV-16.

30 September 2016: Teleconference with Applicant regarding organization of datasets to be submitted for studies DV2-HBV-10 and DV2-HBV-16 in response to the 9 September 2016 IR. Applicant informed CBER that for study DV2-HBV-16 the final disposition of subjects, whether included or merely eligible for inclusion, in the lot consistency per protocol (LCPP) analysis was not clearly indicated in the corresponding ADSL dataset, and therefore it would not be possible for CBER to determine the accurate number of subjects in the LCPP analysis from the dataset. The Applicant agreed to clearly designate subject disposition by adding additional variables to the revised master dataset to be submitted in response to the 9 September 2016 IR.

3 October 2016: CBER received Applicant submissions in response to the 9 September 2016 IR from 26 September - 11 October 2016, including a Major Adverse Cardiovascular Events (MACE) analysis, received on this date, conducted by the Applicant to further evaluate the imbalance noted between study groups in MI.

10 November 2016: Second CR letter issued to the Applicant in order to thoroughly review the information submitted in response to the 9 September 2016 IR, in particular the safety information submitted regarding the differences in MI between study groups and additional SAE narratives, and to obtain expert cardiology consultation on the Applicant's MACE analysis. Outstanding CBER concerns submitted to the Applicant for further clarification comprised the following: subject accounting for the per protocol subjects for studies DV2-HBV-10 and -16, a request for greater detail and information regarding various aspects of the safety review for study DV2-HBV-23, and two BIMO concerns regarding data entry access to Excel spreadsheets, and handling of subjects with protocol deviations, including re-engagement of subjects who were 'lost to follow-up'.

8 February 2017: Applicant's complete response to the November 2016 CR letter received.

28 July 2017: Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held (Section 5.4.1).

2 August 2017: CBER requested a detailed summary of the Applicant's revised pharmacovigilance plan (PVP) incorporating discussion of the VRBPAC.

9 August 2017: CBER received the Applicant's detailed summary of the revised PVP. CBER issued a major amendment based upon this submission.

12 October 2017: Discussion of post marketing requirement (PMR) at Safety Working Group (SWG) meeting. The clinical review team stated its recommendation to not approve Heplisav-B, in part due to the cardiovascular risk that the proposed PMR is supposed to address. Limitations of the proposed post-marketing study were discussed, including selection bias given the observational and non-randomized study design, timeliness of data acquisition based on recruitment capability, and inadequate representation of individuals at greater risk for cardiovascular disease, particularly those of an older age. SWG believed CBER could reasonably mitigate the potential risk associated with vaccine use by both implementing early evaluations for a safety signal at a planned interim analysis timepoint in the PMR study, and through the use of CBER's own planned post-approval safety surveillance efforts.

2.6 Other Relevant Background Information
Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

CBER identified a number of deficiencies during the second review cycle, resulting in CBER's request for additional information from the Applicant and extensions of the review timeline. The 16 March 2016 CR submission did not include datasets for studies DV2-HBV-10 and DV2-HBV-16 to support the revised CSRs. This deficiency resulted in a Major Amendment. The Applicant did not submit a complete listing of subjects newly excluded and newly included into the per protocol population for studies DBV-HBV-10 and -16. The immunogenicity reviewer noted additional subject accounting discrepancies in the information submitted during this second review cycle, despite multiple communications with the Applicant, namely PP subject accounting inconsistencies for DV2-HBV-10 and -16.

Further, the safety reviewer identified concerns and deficiencies regarding the safety data provided in this submission. Prior to the 16 March 2016 submission, the Applicant and the CBER agreed that the Applicant could submit only select serious adverse event (SAE) narratives from DV2-HBV-23, for deaths, AESIs, and any SAEs that were not clearly attributable to another cause. At the time of this discussion, CBER was unaware of additional safety concerns in cardiac SAEs that were identified by the safety reviewer during review of the 16 March 2016 submission. Narratives and case report forms (CRFs) for all cardiac SAEs and additional SAEs of interest were submitted in response to the 9 September 2016 IR; due to the volume of the response as well as the importance of obtaining expert consults, thorough review of this information was deferred to the third review cycle. Narratives and information on additional specific events identified were requested of the Applicant, as well.

The following is a list of additional errors, inconsistencies, or discrepancies noted in the information submitted for DV2-HBV-23:

- Hyperlinks inserted throughout the submission were not functional. Some supportive documents were not located where one would expect.

***Reviewer comment**: The Applicant was asked to ensure that all hyperlinks were correct and functional, which was addressed in the 8 February 2017 CR response.*

- In DV2-HBV-23, 762 subjects who received at least one dose of Heplisav-B and 381 subjects who received at least one dose of Engerix-B were reported to have (flagged as) type 2 diabetes by the investigator. "Diabetic" was defined as a clinical diagnosis of type 2 diabetes and taking a hypoglycemic agent. The primary immunogenicity endpoint was evaluated based on the flagged diabetic population, those who met the criteria for the per protocol population. A reviewer-generated analysis using the dataset ADMH (analysis dataset for medical history) found of subjects flagged as diabetics, 172 Heplisav-B subjects and 93 Engerix-B subjects did not have any history of diabetes or diabetic-related condition recorded in the dataset ADMH.

  ***Reviewer comment:** The potential internal discrepancies with regard to diabetes status suggest there may have been incomplete data collection and quality control in study DV2-HBV-23. However, both treatment groups seem to be affected similarly and the number of subjects affected compared to the overall number of subjects enrolled is low.*

- Start dates for AESIs listed in the dataset ADAE (analysis dataset for adverse events), for which detailed narratives were reviewed, appear to be inconsistently applied. Start dates could represent the date of symptom onset, the date a physician made a final diagnosis even if symptoms started previously, or the first day of the study when the Applicant tested pre-vaccination blood draw to determine an event was pre-existing.

  ***Reviewer comment:** While some variation is expected depending on the nature of the event or diagnosis, similar types of events appeared to have different types of start dates. In the 9 September 2016 IR, the Applicant was asked how investigators were instructed to report start dates. The Applicant responded in 125428/0.63 and included the CRF Completion Guidelines, which do not offer instructions on selecting a start date. The Sponsor notes the statement "A Medically Attended event term is a clinical diagnosis or condition, not a list of symptoms caused by a clinical condition (e.g. enter 'flu' and not 'fever, chills, achy') unless no specific diagnosis is made." They seem to use this statement to justify both a start date of symptom onset and a start date of final diagnosis in two different subjects' MAEs.*

  Upon review of the information submitted by the Applicant, there does not appear to be any systematic method in determining the start date of an AE. In the opinion of the clinical reviewer, the start dates of AESIs in the datasets are sometimes unreliable. The extent to which this occurs for all SAEs and MAEs is unknown. Narratives were reviewed for events of interest, such as AESIs and cardiac events, and when start date discrepancies were noted and pertinent, they are described in this review and considered in an assessment of safety. However, it is possible that an evaluation of safety based on temporal relationship to vaccination could be compromised due to differential start date reporting for events for which narratives were not submitted, particularly for events with insidious onset or that are difficult to diagnose.

- Several entries in the dataset ADAE appear to be the same event listed multiple times when an event progressed from non-serious to serious (for example, subject 118-229 chest pain and angina pectoris). Event terms are the same or similar and the stop date for one event is the same as the start date for the other event. The Applicant was asked to explain the way events were captured in the datasets and provide a list of adverse events that appear in the datasets as two separate events but are described as the same actual event in the 9 September 2016 IR. In 125428/0.68, in response to the 9 September 2016 IR, the Applicant responded that investigators were asked to capture AEs as two separate events when an event changed from non-serious to serious. The Applicant states that the instructions were developed in accordance with the ICH E9 and Clinical Data Acquisition Standards Harmonization (CDASH)/Clinical Data Interchange Standards Consortium (CDISC) implementation guidelines and were consistent with other studies in the BLA. The Applicant identified 19 events that appeared to be the same disease process that was reported as an MAE and an SAE.

  Reviewer comment: *If the same event is listed in multiple entries, the clinical reviewer is unable to determine the number of events per subject. However, the number of events and subjects this appears to affect is low and so, is not likely to significantly affect the evaluation of safety.*

- Dataset ADAE also contained two errors in start date years, which were not noted by the Applicant. The same dataset contained four apparent errors in misclassification of the venous thromboembolism flag, not all of which were identified by the Applicant in their CSR.

  Reviewer comment: *While these errors are not felt to represent systemic problems, they could indicate poor quality control. Correct start dates were submitted in 125428/0.54 in response to an IR sent 28 June 2016.*

Reviewer comment: *Overall, the submission quality was judged to be suboptimal by the clinical reviewers, based upon omissions of datasets and narratives, subject accounting issues, and potential inconsistencies within the datasets (diabetic status, unclear AE start date instructions for investigators). Most of the quality issues were addressed with submission of additional information reviewed during the third review cycle.*

3.2 Compliance with Good Clinical Practices and Submission Integrity
A number of inconsistencies and discrepancies were found during the immunogenicity and safety review of each of the studies provided in this CR (revised studies DV2-HBV-10, -16, and study DV2-HBV-23). Ultimately, DVRPA's concerns regarding good clinical practice (GCP) for studies DV2-HBV-10 and -16 and BIMO's concerns regarding study DV2-HBV-23 (see discussion below) were addressed by the Applicant in the 8 February 2017 complete response.

With respect to revised studies DV2-HBV-10 and -16, a tabular listing of subjects newly excluded from the per protocol populations was not submitted in the 16 March 2016 CR, even though the purpose of the revised CSRs was to provide accurate subject accounting, based on inappropriate inclusion or exclusion of subjects into the per protocol (PP) populations in these two respective studies. Subsequent IR letters issued to the Applicant resulted in IR responses which failed to provide accurate accounting of

newly excluded and newly included subjects for both studies DV2-HBV-10 and -16. Using the subject accounting information provided in the Applicant's second IR response dated 12 July 2016, the clinical reviewer was able to account for the number of newly excluded and newly included per protocol population subjects for study DV2-HBV-10, and the statistical reviewer was able to verify these subjects. Because the Applicant's IR responses were unable to address subject accounting discrepancies for study DV2-HBV-16, additional clarification was sought by CBER.

A subsequent teleconference with the Applicant on 3 August 2016 revealed mislabeling by the Applicant of subjects' non-inferiority and lot consistency per protocol status that would require correction in the .xpt files by the Applicant. A follow-up teleconference on 30 September 2016 also revealed that the Applicant had denoted 'study eligible' subjects as being the same as the 'per protocol population' even though the specific criteria for inclusion and definitions for the two populations were different, as provided by the Applicant in the original protocol and the original and revised CSRs for study DV2-HBV-16. The newly excluded and newly included 'per protocol' subjects provided in the tabular listings for study DV2-HBV-16 in the two IR responses submitted by the Applicant on 27 April 2016 and 12 July 2016 also included 'study eligible' subjects which resulted in uninterpretable subject accounting data. When queried, the Applicant stated that the data for study DV2-HBV-10 did not include this error.

Verification of the immunogenicity data for studies DV2-HBV-10 and -16 was complicated by the Applicant's inclusion of newly excluded subjects only, in the revised .xpt files for study DV2-HBV-10 and -16. During the second review cycle, the statistical reviewer deferred verification of the immunogenicity data from these studies pending resolution of subject accounting discrepancies during the third review cycle.

The persistent inconsistencies in the per protocol subject accounting for studies DV2-HBV-10 and -16 resulted in CBER's request for master datasets for studies DV2-HBV-10 and -16, inclusion of Excel spreadsheets which tracked affected per protocol subjects' status from 2012 to 2016, and listing of newly excluded and newly included per protocol subjects for study DV2-HBV-16, included in the 10 November 2016 CR letter. Additional BIMO findings regarding the per protocol population and inadequate access control to capture protocol deviations for study DV2-HBV-23, were also included as additional CR comments in the November 2016 CR letter.

Data inconsistencies and BIMO concerns were definitively addressed with the Applicant's 8 February 2017 CR, which contained adequate information to verify per protocol subject number and subject accounting for studies DV2-HBV-10 and -16. Using the data provided in the CR, the clinical reviewer was able to confirm that the subject accounting in the revised CSRs for DV2-HBV-10 and -16 was correct. The statistical reviewer verified that the revised immunogenicity analyses for the primary immunogenicity endpoints in both of these studies were accurate and did not differ substantially from the original immunogenicity analysis.

Regarding BIMO concerns for study DV2-HBV-23, the Applicant additionally provided sufficient information for the BIMO reviewer to assess the potential impact of the findings regarding protocol deviations and misclassification of subjects in the per protocol population, the Applicant's procedures for re-engagement of subjects lost-to-follow-up, along with the use of an Excel spreadsheet with inadequate access control. The BIMO reviewer concluded, based on the Applicant's response in the 8 February complete

response, that these were not substantive issues that affected the submitted study data. The BIMO reviewer's final determination was that the BIMO findings affected a small proportion of study subjects for DV2-HBV-23 and did not impact overall GCP compliance for this study. As stated in Section 3.1, narratives and CRFs for all cardiac SAEs reported in DV-HBV-23 were not submitted in the 16 March 2016 response to the CR letter, although the Applicant noted an imbalance in acute myocardial infarction in their CSR.

Reviewer comment: *The Applicant did not specifically discuss these imbalances between the two study groups with CBER prior to the 16 March 2016 submission of the response to the CR letter. The Applicant declined to meet with CBER (Type C pre-submission meeting) prior to the 16 March 2016 CR response documents. How to address issues such as this might have been discussed in such a meeting.*

3.3 Financial Disclosures

Investigators with financial conflicts of interest for studies DV2-HBV-10 and -16 were previously addressed in the original clinical review of this application dated 26 February 2013.

Regarding study DV2-HBV-23, the Applicant provided CBER Form 3455 and a list of 41 investigators and no more than 585 sub-investigators. Some sub-investigators were associated with more than one site and were listed at all sites. Regarding study DV2-HBV-22, the Applicant identified one investigator and nine sub-investigators. The Applicant stated there were no investigators with disclosable financial interests as per 21 Code of Federal Regulations (CFR) 54.2.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls
CBER CMC reviewers identified issues pertaining to drug product manufacturing, in process testing, specifications (e.g. HBs Ag protein content, 1018 adjuvant content, and endotoxin testing), validation, and stability data, which they found were adequately addressed in the Applicant's February 2017 complete response (125428/0.74). Please see CMC reviews for details.

4.2 Assay Validation
In vivo potency assay validation was established during this review cycle. CR comment #48 regarding in vivo potency determination was adequately addressed by the Applicant in the 8 February 2017 CR response (Statistical Review Memorandum, Lei Huang, 25 May 2017).

4.3 Nonclinical Pharmacology/Toxicology
Nonclinical pharmacology/toxicology for the combined recombinant hepatitis B antigen and 1018 adjuvant and for the 1018 adjuvant alone were previously reviewed in the original application for BLA STN 125428/0. Please refer to the reviews of Dr. Steven Kunder dated 21 February 2013 and Dr. Claudia Wrzesinski dated 23 January 2013 for pharmacology/toxicology reviews of Heplisav-B (rHBsAg plus 1018 adjuvant) and the 1018 sequence alone, respectively.

Given the additional safety concerns identified in the second and third review cycles, a summary of non-clinical data focusing on pertinent findings (cardiovascular system and autoimmunity) is presented here.

Non-clinical toxicology studies were conducted with a vaccine similar to Heplisav-B or with 1018 adjuvant alone in a number of rodent and non-human primate (NHP) studies. In a repeat-dose toxicity study, mice were administered three intramuscular doses of a vaccine formulation containing 0.5 mcg HBsAg/mL and 50 mcg 1018 adjuvant/mL (1/40th and 1/60th of the human antigen and adjuvant dose on an absolute basis, respectively). No mortality or clinical toxicity was seen, but mild, transient anemia and associated mild extramedullary hematopoiesis were noted. Microscopically observed epicardial mineralization (a common spontaneous lesion in mice) was reported in animals receiving both adjuvanted antigen and antigen alone. Serology assessment was not performed.

Tissue distribution studies of other phosphorothioate ODNs in mice, rats and primates primarily showed distribution into kidney, liver, lymph nodes, spleen, and bone marrow. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow (measured in days to weeks), because the phosphorothioate backbone resists degradation. Renal clearance is low and elimination from tissues is slow.[20, 21, 22]

In a repeat-dose toxicity study of 1018 adjuvant alone rats were administered 8 subcutaneous doses of 1018 adjuvant at 12.5 mg/kg per dose (the human dose is 3 mg/dose). Transient thrombocytopenia, anemia, lymphocytosis, neutrophilia, and monocytosis, as well as compensatory medullary and extramedullary hematopoiesis were observed. Elevated BUN, renal tubular degeneration, interstitial inflammation and oligonucleotide deposition in the renal proximal tubular epithelial cells was seen, but no effect on renal function and no specific findings of glomerulonephritis or vasculitis were detected. Additionally, congestion, dose-dependent liver atrophy, Kupffer cell hyperplasia and chronic inflammation were observed in the liver; considerable recovery was apparent after the recovery phase. Cardiomyopathy was observed in rats at a similar incidence between treatment and control groups and, given this established background finding in this animal, was assessed as not related to test article.

In another repeat dose toxicity study of 1018 adjuvant alone, cynomolgus macaques received 8 subcutaneous doses of 1018 adjuvant at 12.5 mg/kg per dose (the human dose is 3 mg/dose). Transient leukopenia, neutropenia, and modest increases in activated partial thromboplastin time were observed. Splenomegaly with lymphoid hyperplasia, hyperplasia of the Kupffer cells with blue granular pigment inclusions in the highest dose group and minimal to mild activation of the alternative complement pathway were observed after the treatment phase. These findings in the liver and spleen were still present after a 4-week recovery period but with decreased severity.

In summary, no significant toxicity was observed in the pre-clinical studies and all effects were thought to reflect previously described class effects of oligodeoxynucleotides, as well as the expected immunostimulatory properties of the vaccine.

Reviewer comment: *Non-clinical studies of a vaccine "similar to Heplisav-B" used a dose lower than the human dose on an absolute basis. Non-clinical investigations of the potential for CpGs or Heplisav-B to induce autoimmunity have been suboptimal given the lack of an appropriate mouse or well-characterized non-human primate model of human autoimmunity. Non-clinical investigations to specifically look for cardiac toxicity*

of Heplisav-B were not performed. Cardiac changes that were observed in non-clinical studies were consistent with established background incidences of cardiac findings. No adverse test article-related findings were observed following administration of a lower dose of a vaccine similar to Heplisav-B in an animal model with a background incidence of cardiac findings and following administration of a higher dose of adjuvant alone in two animal models, one with a background incidence of cardiac findings. Additionally, as highlighted by the participating cardiologist on the 28 July 2017 VRBPAC, myocardial infarction is a "vascular disease, and the two primary drivers of myocardial infarction are inflammation, plaque inflammation and thrombosis. So to focus when we look at myocardial infarction is to look at factors that drive inflammation and thrombogenesis."[23] Therefore, the clinical reviewers find that the preclinical data to support Heplisav-B do not inform the finding of myocardial infarctions noted in study DV2-HBV-23 given the inherent limitations of the animal model, the fact that the to be marketed formulation of the vaccine was not used in the preclinical studies, and the lack of specific investigation to evaluate for cardiovascular toxicity.

4.4 Clinical Pharmacology
Clinical pharmacology was previously discussed in the original clinical review of Heplisav-B dated 26 February 2013. Please refer to Sections 4.4 and 4.4.1 in that review for further information.

4.4.1 Mechanism of Action
Heplisav-B consists of rHBsAg and 1018 adjuvant, a synthetic cytosine phosphoguanine oligodeoxynucleotide (CpG ODN) sequence, which is comprised of cytosine and guanine enriched unmethylated single strand DNA sequences. Unmethylated CpG sequences are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9), present on dendritic cells and B cells. Activation of TLR9 receptors stimulates a T helper 1 (Th1) immune response, with secretion of proinflammatory cytokines that activate macrophages, monocytes, and natural killer cells. This activation is thought to result in a high and sustained antibody response, likely due to generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory cells.

In summary, Heplisav-B is proposed to act by using an adjuvant that activates TLR9 in plasmacytoid dendritic cells which, combined with HBsAg, leads to production of HBsAg-specific antibodies.

4.4.2 Human Pharmacodynamics
Human pharmacodynamics and the rationale for dose selection of the 1018 adjuvant for further clinical development and for the candidate vaccine formulation was previously addressed in the original clinical review dated 26 February 2013.

4.4.3 Human Pharmacokinetics
Not applicable.

4.5 Statistical
CBER statistical reviewers noted the data suggested an elevated risk of AMI associated with Heplisav-B compared with Engerix-B and that this warranted further investigation, preferably prior to licensure of Heplisav-B, as the data do not support safety of the Heplisav-B vaccine. Dr. Xiang generally confirmed the Applicant's immunogenicity analyses.

4.6 Pharmacovigilance
During the third review cycle, Dr. Perez-Vilar noted concerns with the adequacy of the pharmacovigilance plan to detect an increased risk of myocardial infarction in the post-marketing setting. Please refer to Dr. Said's review regarding the second review cycle and Dr. Perez-Vilar's review for the third review cycle.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy
Dr. Alexandra Worobec reviewed revised primary immunogenicity data from studies DV2-HBV-10, and DV2-HBV-16, and immunogenicity data in the type 2 diabetic population (the pre-specified primary immunogenicity endpoint) in study DV2-HBV-23. Immunogenicity data in the overall per protocol population and in demographic subgroups was also reviewed in DV2-HBV-23. Study DV2-HBV-23 immunogenicity data (as assessed using the SPR) were reviewed to establish non-inferiority between Heplisav-B and the active comparator, Engerix-B, and to show that the immunogenicity data in each of these populations were similar to the SPR data seen in studies DV2-HBV-10 and -16.

Complete subject accounting data were included in the 8 February 2017 CR response (including Excel spreadsheets which tracked the status of each newly excluded and newly included subject from 2012 to 2016). Using these data, Dr. Worobec was able to verify subject accounting of the PP populations in studies DV2-HBV-10 and -16, and Dr. Xiang verified the revised immunogenicity results of studies DV2-HBV-10 and -16.

Dr. Darcie Everett reviewed safety data from study DV2-HBV-23, as well as an integrated analysis in which the Applicant incorporated safety data from all of the studies evaluating Heplisav-B. CBER's analysis focused on SAEs and integrated studies DV2-HBV-23, -10, -16, -14, and -22, studies in which subjects received the final formulation and schedule of the candidate vaccine. CBER's analysis of AESIs included review of AESIs from all the studies submitted in support of licensure. Safety from pivotal and supportive studies submitted in support of the original BLA, including from studies DV2-HBV-10 and -16 were not re-reviewed with the exception of when information was directly pertinent to safety issues identified in the second and third review cycles and information that was pertinent to the Applicant's complete response. Please refer to the original clinical review dated 26 February 2013 for these details. However, SAEs and AESIs from the above studies were considered in the context of the ISS. Consequently, with regard to safety data, only study DV2-HBV-23 was reviewed in Section 6 for the second and third review cycles. DV2-HBV-22 was not included in the clinical review of the initial BLA submission and was not reviewed in Section 6 because it was a small, uncontrolled supportive study, in which no SAEs or AESIs were reported. Subjects in study DV2-HBV-22 were also included in the ISS.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review
The following sections of 125428/0.42 were assigned to and reviewed by the Clinical Reviewers:

- 1.2 Cover Letters
- 1.3.4 Financial Certification and Disclosure
- 1.9.1 Request for Waiver of Pediatric Studies
- 1.11.3 Clinical Information Amendment

- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5.2 Tabular Listing of all Clinical Studies
- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertaining to the Claimed Indication
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.4 Literature References

The following additional amendments prior to the 16 March 2016 submission were submitted incrementally in response to the 22 February 2013 CR letter, contained safety information requested in the CR letter regarding individual subjects, and were reviewed in the second review cycle:

- 125428/0.34 Modules 1.2, 5.3.5.1
- 125428/0.35 Modules 1.2, 5.3.5.1

The following amendments received following the 16 March 2016 submission were reviewed by the Clinical Reviewers in the second review cycle and contained response to safety and immunogenicity IRs:

- 125428/0.45 Modules, 1.11.3, 5.3.5.1
- 125428/0.49 Modules 1.11.3, 5.3.5.1
- 125428/0.54 Modules 1.11.3, 5.3.5.1

The following amendments received following the 16 March 2016 submission, prior to the 8 February 2017 submission were reviewed by the Clinical Reviewers in the third review cycle and contained substantial safety and immunogenicity information in response to the 9 September 2016 IR:

- 125428/0.63, Modules 1.11, 5.3.5.1
- 125428/0.65, Modules 1.11, 5.3.5.3
- 125428/0.67, Modules 1.11, 5.3.5.1
- 125428/0.68, Modules 1.11, 5.3.5.1
- 125428/0.69, Module 5.3.5.1

The following sections of the February 2017 CR submission 125428/0.74 were reviewed by the clinical reviewers:

- 1.2 Cover Letter
- 1.6 Meetings
- 1.11.3 Clinical Information Amendment
- 1.16 Risk Management Plan
- 2.7 Clinical Summary
- 5.2 Tabular Listing of all Clinical Studies
- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertaining to the Claimed Indication
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.4 Literature References

The following amendments received following the 8 February 2017 submission were reviewed by the Clinical Reviewers in the third review cycle and contained safety information submitted in response to IRs:

- 125428/0.87 Module 1.11.3

- 125428/0.88, Modules 1.11, 5.3.5.1
- 125428/0.94 Module 1.11.3
- 125428/0.105 Modules 2.7.4, 5.3.5.3

The clinical reviewers provided clinical input on the following amendments regarding labeling discussions, which were ongoing at the time this document was finalized:

- 125428/0.97, Module 1.11, 1.14
- 125428/0.99, Module 1.11
- 125428/0.103, Module 1.11, 1.14, 5.3.5.1
- 125428/0.109, Modules 1.11, 1.14, 5.3.5.3
- 125428/0.110, Module 1.11, 1.14

The clinical reviewer deferred primary review of the pharmacovigilance plan to Dr. Perez-Vilar; however, the clinical reviewers provided clinical input on the following amendments regarding the pharmacovigilance plan and post-marketing studies, discussions of which were ongoing at the time this document was finalized:

- 125428/0.86, Module 1.11
- 125428/0.90, Module 1.11
- 125428/0.91, Module 1.11
- 125428/0.93, Module 1.11
- 125428/0.95, Module 1.11
- 125428/0.96, Module 1.11
- 125428/0.98, Module 1.11
- 125428/0.100, Module 1.11
- 125428/0.102, Module 1.11
- 125428/0.104, Module 1.11

5.3 Table of Studies/Clinical Trials

Table 1. Summary of the studies using the proposed formulation of Heplisav-B for the immunogenicity and safety analyses in this review

Study Name	Study Design	Heplisav-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-10 Pivotal NCT00435812	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in healthy subjects 11-55 years of age conducted in Canada and Germany	Heplisav-B: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1810*	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=605*	Primary Endpoint: SPR at Week 12 for Heplisav and Week 28 for Engerix-B Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs/SAEs study Week 28

Study Name	Study Design	Heplisav-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-16 Pivotal NCT01005407	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in healthy adult subjects 40-70 years of age conducted in Canada and the U.S.	Heplisav-B: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1968	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=481	Primary Endpoint: SPR at Week 12 for Heplisav-B and Week 32 for Engerix- B Lot consistency of Heplisav-B measured by GMC at Week 8 Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs study Week 28, SAEs/AESIs study Week 52
DV2-HBV-23 Pivotal NCT02117934	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in adults 18-70 years of age conducted in the U.S.	Heplisav-B: 20 mcg HBsAg/3000 mcg 1018 adjuvant adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N = 5587	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N = 2781	Primary Efficacy Endpoint: SPR at Week 28 in subjects with type 2 diabetes mellitus Secondary Efficacy Endpoint: SPR at Week 24 for Heplisav-B and Week 28 for Engerix-B Major Safety Endpoints: MAEs/SAEs/AESIs study Week 56
DV2-HBV-14 NCT00511095	Phase 2, multicenter, open label, single-arm study in healthy subjects 11-55 years of age conducted in the U.S.	Heplisav-B: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM N=207	None	Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs/SAEs study Week 28

Study Name	Study Design	Heplisav-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-22 NCT01999699	Single-center, open-label, single group trial in healthy adults 50-70 years of age in the U.S.	Heplisav-B: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM N = 25	None	Major Safety Endpoints: AEs study Week 12, SAEs/AESIs study Week 56

Source: Adapted from STN 125428/0.42, module 5.2 Tabular Listing of All Clinical Studies and module 2.7.4 Summary of Clinical Safety, Table 2.7.4-1, p. 16 – 20
N: number of subjects in the Safety Population
mcg: micrograms
HBsAg: hepatitis B surface antigen
IM: intramuscular
SPR: seroprotection rate
AE: adverse event
SAE: serious adverse event
GMC: geometric mean concentration
AESI: adverse event of special interest
MAE: medically-attended adverse event
* One subject in study DV2-HBV-10 was randomized to Engerix-B and treated with Heplisav-B. This subject is included in the Heplisav-B group in this review, but was included in the Engerix-B group in previous reviews.

5.4 Consultations

5.4.1 Advisory Committee Meeting

Please refer to the original clinical review and transcript[19] for details of the VRBPAC meeting held on 15 November 2012. The immunogenicity and safety data for the original BLA review were presented at this meeting. At the conclusion of this meeting, the committee raised concerns that the safety database was insufficient to recommend approval of Heplisav-B. VRBPAC members voted 13:1 that the data submitted in the BLA adequately demonstrated the immunogenicity of Heplisav-B. However, the Committee voted 8:5, with one abstention, that inadequate safety data were available to recommend approval of Heplisav-B. The VRBPAC also noted that the studies did not evaluate the vaccine in a racially heterogeneous population of subjects who were most likely to benefit from this vaccine and that concomitant administration studies were not done.

Another VRBPAC meeting was held on 28 July 2017 to discuss the results of DV2-HBV-23 and the overall risk/benefit profile of Heplisav-B.[23] The committee voted 12:1 with 3 abstentions that the available data was adequate to support the safety of Heplisav-B when administered to adults 18 years and older. Committee members commented that the difference in frequency of MI between treatment groups was likely a spurious result, that the potential benefits outweighed the potential risks, and that a well-designed study to evaluate the cardiovascular risk associated with Heplisav-B in a population that includes subjects at risk for cardiovascular disease was necessary. Specific aspects of such a safety study were also discussed.

5.4.2 External Consults/Collaborations

Review of the initial BLA submission in 2012 identified one subject with a potential granulomatous vasculitis adverse event following Heplisav-B in study DV2-HBV-16. Review of the initial BLA submission in 2012 identified one subject with a potential

granulomatous vasculitis adverse event following Heplisav-B in study DV2-HBV-16. The subject was diagnosed with possible Tolosa-Hunt syndrome (THS), reported as verbatim term cavernous sinus syndrome, preferred term cavernous sinus thrombosis, in study DV2-HBV-16. Additional information was requested in CR letter item #3 and was submitted in STN 125428/0.33, received 18 March 2013. CBER sought internal and external consultation to provide expert opinion on the diagnosis and relationship to the vaccine, which was pending at the time the February 2013 CR letter was issued. See below for a summary of the case and expert consultations. Please see the Appendix for the complete consultations.

Subject 40-616 was a 69-year-old male Heplisav-B recipient, with multiple medical issues, who developed "amblyopia" approximately six months after the second injection of Heplisav-B, followed by severe headaches, later associated with diplopia. He was also noted to have severe ptosis and left cranial nerve VI palsy. The subject's symptoms were acutely responsive to each of several courses of steroids with symptoms returning upon discontinuation. A diagnostic evaluation, which included multiple imaging studies, was negative. More than nine months following the second study injection, the subject was diagnosed with THS, a painful ophthalmoplegia caused by a non-specific granulomatous inflammation of the cavernous sinus of unknown etiology with potential vasculitic or other autoimmune etiology. No tissue diagnosis was obtained, nor is it necessary to diagnose THS. Anti-neutrophil cytoplasmic antibody (ANCA) testing is often negative. Following resolution of the event, the treating neurologist changed the diagnosis from THS to cavernous sinus syndrome. The investigator assessed the event of cavernous sinus syndrome as severe in intensity and not related to study treatment. Four CBER specialist consultants assessed the case as THS, each of them noting the response to steroids and reasonable exclusion of alternate etiologies. Of the three consultants that commented, two did not believe that there was evidence of overlap between THS and GPA. One consultant noted that there can be overlap, but that this case of THS did not have features that would be expected if it were GPA. One consultant was concerned given the rarity of GPA and THS that they were observed in a trial population of this size. However, none of the consultants endorsed a clear causality between the CpG-containing vaccine and the immune-mediated event.

Reviewer comment: *This case is considered by the clinical reviewer to be a new-onset AESI, the second rare (incidence 1 in 1 million person years) presumed granulomatous vasculitis identified within the Heplisav-B safety database.*

In the second review cycle, two experts were consulted regarding a case of newly diagnosed Takayasu arteritis reported in a Heplisav-B recipient in study DV2-HBV-23; full review of these consults is found in Section 6.3.

In the third review cycle and in order to evaluate the Applicant's analysis of major adverse cardiovascular events (MACE) submitted in 125428/0.65, CBER consulted three cardiologists. All three agreed that the Applicant had performed reasonable analyses to attempt to evaluate this risk. Specific critiques noted by the consultants of the various analysis methods are included in the discussion of analyses in Section 8.4.2. Two of the three consultants determined that the imbalance was a concern, noting that it was "moderately concerning" or "infrequent, but troubling." The other consultant determined that there was a low likelihood that this imbalance was a safety signal and that there was a low absolute risk. Two of the three consultants noted that the imbalance was not statistically significant. All three of the consultants noted that further

evaluation is warranted, one specifying that “randomized comparisons and/or large post market observational studies with appropriate collection of suspected events, ECGs, biomarkers and other records needed for event adjudication” would be required and one recommending post-marketing surveillance of risk through a passive surveillance system such as Sentinel.

Reviewer comment: *Several problems exist with concluding that lack of statistical significance equates with lack of a safety signal or concern including: 1) statistical significance is generally not how safety signals are assessed; because the study was not designed to evaluate the risk of a specific AE following vaccination, the absence of statistical significance does not mean there is evidence of no increased risk, and thus, some signals can be concerning even if not statistically significant, and 2) the statistical reviewers recommended a different method of calculating CIs in this setting than what was presented as “conventional” by the Applicant. When using the recommended method, the confidence intervals for some elements of the MACE analysis do not cross 1 (see Section 6.3.12.4 and 8.4.2).*

Internal discussions determined that a post-marketing study to evaluate the cardiovascular risk associated with Heplisav-B could not be efficiently conducted using Sentinel.

The clinical reviewer considered the consultants’ conclusions as part of the totality of the data in the clinical reviewers’ risk benefit assessment and conclusions.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

A Phase 3 Safety and Efficacy Study to Compare Immune Responses following Injection with Either Two Doses of Heplisav-B or Three Doses of Engerix-B (Protocol DV2-HBV-10; NCT00435812)

Reviewer comment: *The March 16, 2016 complete response (CR) submission included a CSR for study DV2-HBV-10 that the Applicant had revised to correct errors detected in an audit of this study, performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA.*

The objectives, study design, immunogenicity endpoints, safety monitoring procedures and safety analysis of study DV2-HBV-10 were previously reviewed with the original BLA of Heplisav-B dated 26 February 2013.

During the second review cycle (following the March 2016 CR), the revised immunogenicity data for this study were reviewed but could not be verified, despite several attempts. The immunogenicity dataset submitted with the revised CSR for DV2-HBV-10 did not include newly included subjects in the per protocol population, which was necessary for an accurate determination of the revised immunogenicity data. Subject accounting and immunogenicity data were verified during the third review cycle (following the CR response dated 8 February 2017).

Reviewer comment: *Dynavax submitted a corrected master dataset and detailed accounting of subjects reassigned into and out of the per protocol population under STN 125428/0.66 on 8 October 2016. The Applicant resubmitted these data with the second CR response dated 8 February 2017.*

6.1.1 Objectives

Objectives of study DV2-HBV-10 were previously detailed in the original BLA review of Heplisav-B dated 26 February 2013.

Briefly, the primary immunogenicity objective of this study was to compare the proportion of subjects who exhibit a seroprotective immune response (SPR, defined as: anti-HBsAg antibody levels greater than or equal to 10 mIU/mL) when measured at Week 12 following vaccination with Heplisav-B at 0 and 1 months, to the proportion of subjects who exhibit SPRs when measured at Week 28 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months.

The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with Heplisav-B when administered to adolescent and adult subjects.

6.1.2 Design Overview

Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0 dated 26 February 2013 for a detailed description of the trial design.

Briefly, this phase 3 study was a subject- and observer-blinded, randomized, controlled study of approximately 2400 subjects, 11-55 years of age (ages 18-55 in Germany) conducted at 21 sites in Canada and Germany. Subjects were randomized 3:1 to

receive vaccination with Heplisav-B (20 mcg recombinant HBsAg and 3000 mcg 1018 adjuvant) or Engerix-B vaccine (20 mcg recombinant HBsAg and 50 mcg Alum adjuvant). Subjects were stratified by age (11 to 39 years of age versus 40 to 55 years of age) prior to randomization. Subjects randomized to Engerix-B received three injections of Engerix-B, at Weeks 0, 4 and 24. Subjects randomized to Heplisav-B received Heplisav-B vaccinations at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4 (1 month), and Week 24 (6 months). The duration of the study was 28 weeks.

Reviewer comment: *Because of the different volume and appearance of study vaccines administered, the pharmacist or nurse that prepared the injection, as well as the physician or nurse who administered the injection, may have been aware of the vaccine assignment of each subject. In an effort to decrease bias in evaluating reactions to the vaccines, the investigator and study staff working with the subjects and the subjects themselves were to remain unaware of the treatment assignment. Given the caveats of a difference in the volume delivered per vaccination and solution appearance between the Heplisav-B and Engerix-B vaccines, an observer-blinded study was appropriate.*

6.1.3 Population
The study population comprised HBV seronegative male and female subjects. The major inclusion and exclusion criteria are listed below:

Inclusion Criteria:

- At least 11-55 years of age (at least 18 and up to 55 years of age for Germany).
- Serum negative for HBsAg, anti-HBsAg antibody and anti-HBcAg antibody.
- Childbearing age females: appropriate practice of birth control for the duration of the study.

Exclusion Criteria (select):

- Any history of HBV infection.
- Prior immunization with any HBV vaccine (one or more doses).
- History of or laboratory evidence of diseases of autoimmune origin.
- At high risk for recent exposure to HBV, HCV or HIV, e.g. current intravenous (IV) drug use, unprotected sex with known HBV, HCV or HIV positive partner.
- Clinically debilitating acute or chronic disease (including fever greater than or equal to 38˚ C within 72 hours prior to study injection) and current substance or alcohol abuse.

Reviewer Comment: *Subject inclusion and exclusion criteria were appropriate.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to the Heplisav-B group received a total of two injections of Heplisav-B, (20 mcg of rHBsAg and 3000 mcg of 1018 HBsAg), manufactured by Rentschler BioTechnologie GmbH, Laupheim, Germany. The rHBsAg component of Heplisav-B was derived from yeast cells transformed with an expression vector containing HBsAg ((b) (4) sequence, subtype *adw*. The 1018 adjuvant is a 22-mer cytosine phosphoguanine (CpG) enriched oligonucleotide with the sequence: 5' TGA CTG TGA

ACG TTC GAG ATG A 3' and which is a toll-like receptor 9 agonist and immunostimulant. The only lot number of Heplisav-B used in this study was TDG003.

Engerix-B (20 mcg HBsAg combined with 50 mcg alum adjuvant, GlaxoSmithKline Biologicals) was used as the active comparator in this study and dosed according to the manufacturer's instructions. The lot numbers used for this study were: AHBVB247AE, AHBVB294AA, AHBVB247AF, AHBVB306AB, AHBVB357DH, AHBVB306AC, AHBVB306AD, AHBVB247AG, AHBVB277AI, AHBVB233BA, AHBVB356AE, AHBVB305AB, AHBVB306AA, AHBVB306AE, AHBVB300AC, AHBVB339AK, and AHBVB297AA.

6.1.5 Directions for Use
Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013.

Injections of Heplisav-B were administered at Week 0 and 4. Each injection was given intramuscularly (IM) into the deltoid muscle of either arm using a 1 to 1.5 inch, 25-gauge needle. The arm used for injection was alternated with each injection. Total injection volume was 0.5 mL to deliver 20 mcg of HBsAg and 3000 mcg of 1018. For the third injection at Week 24, Heplisav-B group subjects received placebo (0.9% sterile saline for injection), administered in 0.5 mL in the same manner as the 1018 HBsAg.

Subjects in the Engerix-B group received three injections, given as a 1.0 mL injection using a 25-gauge needle administered IM into the deltoid muscle, at Weeks 0, 4, and 24. Alternate arms were used with each subsequent injection.

6.1.6 Sites and Centers
Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013.

This phase 3 study was conducted at 14 sites in Canada and 7 sites in Germany. The principal investigator was Scott Halperin, M.D., at Dalhousie University, Nova Scotia, Canada.

6.1.7 Surveillance/Monitoring
Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013 for a detailed Study Schedule.

Briefly, at study Week 0, and subsequently at Weeks 4, 8, 12, 24, and 28 subjects returned to the study site to have blood drawn for quantitative measurement of anti-HBsAg concentrations and for evaluation of safety and tolerability. The immune response (anti-HBsAg) was measured using the (b) (4) .

6.1.8 Endpoints and Criteria for Study Success
The primary immunogenicity endpoint was the between group difference SPR, as measured at Week 12 for Heplisav-B and Week 28 for Engerix-B.

Success criteria were defined as: an upper 2-sided 95% CI limit around Engerix-B SPR - Heplisav-B SPR > +10%.

The secondary immunogenicity endpoint was the SPR at Week 4, which was measured four weeks after the first injection for both treatment groups.

Exploratory analyses evaluated the SPR for Heplisav-B vs. Engerix-B at all other serologic time points (Weeks 8, 12, 24, and 28).

6.1.9 Statistical Considerations & Statistical Analysis Plan

For the statistical analysis plan of study DV2-HBV-10, please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013 and statistical review dated 29 January 2013, respectively. There were no significant revisions to the statistical analysis in the revised CSR received 16 March 2016, using the revised PP population.

The statistical analysis, as submitted in the Applicant's CR received 16 March 2016, was based on the original statistical assumptions and hypothesis testing provided in the original BLA submission dated 26 April 2012 but used the revised non-inferiority per protocol (PP) populations for Heplisav-B and Engerix-B provided with the March 2016 submission in the determination of the revised primary and secondary immunogenicity endpoints and non-inferiority comparison between the two vaccine groups.

Reviewer comment: *The analysis of the primary and secondary immunogenicity endpoints was based on the PP population, so a revision in this subject population could theoretically impact the final results for these two endpoints and conclusions of study DV2-HBV-10. Adequate information was provided by the Applicant in the 8 Feb 2017 CR response to allow CBER to confirm the Applicant's revised results for the primary immunogenicity endpoint in study DV2-HBV-10.*

6.1.10 Study Population and Disposition

A total of 2910 subjects were screened for this study and 2428 enrolled. Thirteen subjects were adolescents (< 18 years): 11 subjects randomly assigned to the Heplisav-B group and two subjects assigned to Engerix-B. The remaining 2415 subjects were adults, including 1809 subjects randomized to Heplisav-B and 606 subjects randomized to Engerix-B.

6.1.10.1 Populations Enrolled/Analyzed

Two populations were considered for the immunogenicity analysis in study DV2-HBV-10:

1. The Per-Protocol (PP) Population: defined as subjects who met the eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had anti-HBsAg measurements and all injections within the specified day ranges, and had an anti-HBsAg measurement at their primary endpoint.

2. The modified intent-to-treat (mITT) Population: defined as subjects who received at least one study injection and had at least one post-baseline anti-HBsAg level.

The immunogenicity analysis using the PP population was considered primary. The baseline value was defined as the last non-missing measurement prior to the first vaccination.

There was no imputation of missing anti-HBsAg data at any visit. If a subject had a missing anti-HBsAg result at a primary endpoint, that subject was excluded from the PP population. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL, as per the SAP.

Reviewer comment: *The clinical reviewer agreed that missing data should not be imputed for immunogenicity analyses. Using the revised subject disposition data for determination of the primary immunogenicity and secondary immunogenicity endpoints, data are presented using the revised per protocol (PP) population, as submitted by the Applicant in the second CR dated 8 February 2017.*

6.1.10.1.1 Demographics
Subject demographics did not change as a result of re-classification of subjects in the non-inferiority PP population.

Subject demographics for the revised CSR are summarized in Table 2

Table 2: Summary of Demographic and Baseline Characteristics for Study DV2-HBV-10: Safety Analysis Population: Adults Only (Subjects 18 – 55 years of age)

Characteristic	Heplisav-B (N=1810) n (%)	Engerix-B (N=605) n (%)	Total (N=2415) n (%)
Age, years, n (%)			
18-39	819 (45.2%)	274 (45.3%)	1093 (45.3%)
40-55	991 (54.8%)	331 (54.6%)	1322 (54.7%)
Mean (SD)	39.9 (9.4%)	39.8 (9.0%)	39.9 (9.3%)
Range	18-55	18-55	18-55
Gender, n (%)			
Male	853 (47.1%)	261 (43.1%)	1114 (46.1%)
Female	957 (52.9%)	344 (56.8%)	1301 (53.9%)
Race, n (%)			
White	1691 (93.4%)	555 (91.7%)	2246 (93.0%)
Black or African American	39 (2.2%)	20 (3.3%)	59 (2.4%)
Asian	43 (2.4%)	22 (3.6%)	65 (2.7%)
American Indian or Alaska Native	16 (0.9%)	3 (0.5%)	19 (0.8%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0	1 (0.0%)
Other	20 (1.1%)	5 (0.8%)	25 (1.0%)
Ethnicity, n (%)			
Hispanic or Latino	46 (2.5%)	24 (4.0%)	70 (2.9%)
Non-Hispanic or Non-Latino	1764 (97.5%)	581 (96.0%)	2345 (97.1%)
Baseline Serostatus, n (%)			
Negative	1798 (99.3%)	604 (99.8%)	
Positive	6 (0.3%)	0	
Unknown	3 (0.2%)	1 (0.2%)	nc

N= Safety population n= number of subjects reporting the specific characteristic,
nc= not calculated, nd = not done, SD = standard deviation
Seronegative to hepatitis B corresponds to antibody level < 5 mIU/mL.
Seropositive to hepatitis B corresponds to antibody level ≥ 5 mIU/mL.
Source: *BLA 125428/0, DV2-HBV-10, CSR, Table 10-4, pages 56-57 of 204, BLA 125428/0.42, DV2-HBV-10, Revised CSR, Table 10-4, pages 57-58 of 442.*

Demographic and baseline characteristics were similar between the two treatment groups. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 40 years, and the percentage of females was slightly higher than that of males. The breakdown by age stratum was similar between the two treatment groups, with slightly more subjects in the 40 through 55-year old subgroup (991 and 331 subjects, respectively for Heplisav-B vs. Engerix-B) than the 18 through 39-year old subgroup (9819 and 4274, respectively, Heplisav-B vs. Engerix-B). More than 99% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL at baseline. Subjects were also categorized by weight, height, body mass index, and smoking status as exploratory variables. No significant differences between the two treatment groups were seen for these characteristics. The majority of enrolled study subjects (63-64% for both treatment groups) were non-smokers, non-diabetic (97%), and non-obese (defined as a BMI ≥ 30 kg/m^2 for both treatment groups; 72-75% non-obese by this definition).

Reviewer Comment: *With the exception of ethnicity and race (the majority of subjects were Caucasian), the study was well-balanced in terms of age strata and gender. The two treatment groups were comparable in terms of demographic characteristics. Greater than 99% of subjects enrolled in the study were seronegative for hepatitis B.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The Applicant's revisions to the PP population had no significant effect on subject characterization by underlying medical conditions or medication use, in either study group. Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013.

6.1.10.1.3 Subject Disposition

The change in the PP population was primarily due to subjects who were evaluated retrospectively (post-hoc) as having a pre-existing autoimmune disorder (PEAI) and who should have been excluded from the PP population in the original immunogenicity analysis based on pre-specified inclusion criteria.

Of the 63 subjects newly excluded from the PP population, 59 subjects were determined post-hoc to have pre-existing autoimmune disease. Psoriasis was the most common autoimmune disorder reported for newly excluded subjects (n=34). The other four subjects newly excluded from the PP population comprised three subjects who were 'dosed incorrectly' with vaccine and one subject with an unreported pregnancy.

Of the five subjects who were originally excluded from the PP population and should have been included, four subjects originally diagnosed with a PEAI did not have an autoimmune disorder and one subject labelled as being pregnant was not pregnant. Two of these subjects were randomized to the Heplisav-B group and three were randomized to Engerix-B, as stated in the Applicant's 12 July 2016 IR response.

Reasons cited for exclusion from the PP population in the re-analysis of study DV2-HBV-10 were (in order of decreasing frequency): pre-existing autoimmune disease, administration of incorrect study treatment for vaccine dose 3, and pregnancy.

Reviewer comment: *A review of the individual subjects excluded from the PP population in study DV2-HBV-10 by the clinical reviewer, including clarifying information*

provided in an Excel spreadsheet provided in the second CR dated 8 February 2017, confirmed a net decrease of 58 subjects from the revised PP analysis. This net decrease was also confirmed by the statistical reviewer using the corresponding .xpt files provided by the Applicant in the 8 February 2017 CR.

All subjects who should have been excluded from or included in the PP population were listed and accounted for. The reasons for exclusion or inclusion of subjects in the newly revised PP population were appropriate, given the pre-defined criteria for study exclusion and major protocol deviations that would have excluded subjects from the PP population.

Select subject disposition data for study DV2-HBV-10, with revised subject accounting for the PP population, are presented in the Table 3 below. Based on the revised PP population, as submitted in the Applicant's CR received 16 March 2016, and re-affirmed in the Applicant's CR dated 8 February 2017, only the PP population changed in the subject disposition analysis. All other subject populations remained the same, including the safety population.

Table 3: Subject Accounting for Study DV2-HBV-10 using the Revised Per-Protocol Population: Adults 18-55 years of age

Study Populations	**Heplisav-B (n)**	**Engerix- B (n)**	**Total (n)**
Randomized Population	1809	606	2415
Original PP Population	1557	533	2090
Total Number of Subjects excluded from the Randomized Population (n, % of randomized population)	252 (13.9%)	73 (12%)	325 (13.5%)
Revised PP Population	1511	521	2032
Net number of subjects excluded in the PP Population in the Revised Analysis	46	12	58
Percentage of Subjects from the Original PP Population Excluded in the Revised PP Population	46/1557 (3.0%)	12/533 (2.3%)	58/2090 (2.8%)
Total Number of Subjects in the Revised PP Population excluded from the Randomized Population (n, % of randomized population)	298 (16.5%)	85 (14.0%)	383 (15.9%)
Total Number of Subjects Newly Excluded from the PP Population	48	15	63
Exclusion due to Pre-existing Autoimmune Disease	44	14	58
Exclusion due to Incorrect Study Treatment for Dose 3	3	0	3
Exclusion Due to Pregnancy	1	1	2
Total Number of Subjects Incorrectly Excluded from the Original PP Population (Included in the Revised PP Population)	2	3	5
Inclusion due to Absence of Pre-existing Autoimmune Disease	1	3	4
Inclusion due to Absence of Pregnancy	1	0	1
Completed	1746 (96.5%)	588 (97.0%)	2334 (96.6%)

Study Populations	Heplisav-B (n)	Engerix- B (n)	Total (n)
Intent-to-treat analysis population	1789 (98.9%)	603 (99.5%)	2392 (99.0%)
Safety analysis population	1810 (100.0%)	605 (100.0%)	2415 (100.0%)

N= Safety population; one Engerix-B subject received Heplisav-B.
Table compiled from: *BLA 125248/0.42, DV2-HBV-10, Revised CSR, Section 16.2.3., pages 1-97, Table 10-1, page 257; BLA 125428/0.47, IR Response, pages 1-23; BLA 125428/0.52, IR Response, pages 9-21, BLA 125428/0.66, Attachments 24c4-24c6, pages 39-42, BLA 125428/0.72, Attachments 24c4-s4c6, pages 39-42.*

Reviewer comment: *While the reasons for study exclusion appear appropriate in this re-analysis of study DV2-HBV-10, the Applicant's inability to identify study subjects who were clearly study ineligible (for example: pre-existing autoimmune disease), until an external event (audit of unrelated study of Heplisav-B by another regulatory agency), raises questions about conduct of this study. Despite revisions to the per protocol population, the immunogenicity outcomes were not significantly changed from the original review of the data, and therefore these data support evidence of effectiveness of Heplisav.*

The revision of the PP population did not change the number of all adult subjects who completed the study (approximately 97% of all adult subjects). The most common reason for subject discontinuation was 'lost to follow-up', reported by 1.7% of subjects in each group. Additional reported reasons for discontinuation were AEs, subject noncompliance, and subject withdrawal of consent.

Reviewer comment: *The revision in the net number of subjects assigned to the PP population had no impact on the other subject disposition categories. The total proportion of subjects excluded from the PP population represented a small proportion of the total PP population (2.8% for Heplisav-B and Engerix-B combined).*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoint for study DV2-HBV-10 was defined as the SPR at Week 12 following two injections of Heplisav-B compared with the SPR at Week 28 following three injections of Engerix-B, using the PP population of adult subjects 18-55 years of age.

The SPR with re-analysis remained unchanged at 95.0% for the Heplisav-B group at Week 12 and increased from 81.1% in the original analysis to 81.2% for the Engerix-B group at Week 28, using the revised PP population. The SPR difference with re-analysis changed from -13.9% to -13.7%. The upper bound of the 95% CI changed from -10.6% to -10.4% and met the primary endpoint of non-inferiority defined as the upper bound of the 95% CI being less than 10%. The impact of the revised number of PP subjects on the primary immunogenicity endpoint was negligible.

These data are presented in tabular form in Table 4.

Table 4: Revised Primary Immunogenicity Endpoint Analysis for Study DV2-HBV-10: SPR for Heplisav-B (Week 12) compared with Engerix-B (Week 28) for the Per-Protocol Analysis Population (Adults 18-55 years of age)

Visit	Heplisav-B[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Engerix-B –Heplisav-B) (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
Week 12/ Week 28	95.0 % (1436/1511)	81.2 % (423/521)	-13.7 (-17.5, -10.4)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatmentgroup, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.
[d] Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).
Source: *BLA 125428/0.42, DV2-HBV-10, Revised CSR, Table 11-1, page 278.*

The Applicant's second IR response submitted to CBER on 12 July 2016 clarified that the timing of reclassification of the PP population occurred on 8 April 2014 (the date of change in population status for reclassified subjects in study DV2-HBV-10).

Reviewer comment: *During the second review cycle, the Applicant provided .xpt files that did not include 'newly included subjects'. Therefore, the CBER statistical reviewer deferred verifying the Applicant's primary immunogenicity analysis during the second review cycle. During the third review cycle, using the corrected dataset, the CBER statistical reviewer was able to verify the primary immunogenicity endpoint. Both the clinical reviewer and the statistical reviewer concluded that the revised PP population had no significant effect on the primary immunogenicity endpoint conclusion. Please refer to the CBER statistical review for details.*

6.1.11.2 Analyses of Secondary Endpoints

One secondary immunogenicity endpoint was pre-defined for study DV2-HBV-10 — the SPR at Week 4, for both the Heplisav-B and Engerix-B PP adult population (age 18-55 years).

With the revised non-inferiority PP population, the SPR at Week 4 changed from 23.6% for Heplisav-B in the original analysis to 23.5% with the revised analysis and from 4.0% for Engerix-B in the original analysis to 4.1% with the revised analysis, respectively. The estimated difference between the Engerix-B and Heplisav-B groups and the associated 95% CI changed from -19.7% (CI: -22.4, -16.8) in the original analysis to -19.5 (CI: -22.2, -16.6) with the revised analysis, respectively. Because the upper limit of the CI was below the pre-specified non-inferiority criterion of +10%, the immune response at the Week 4 time point for Heplisav-B was found to be non-inferior to that of Engerix-B. Secondary immunogenicity endpoint analysis showed a negligible effect of the revised PP population on the SPR four weeks after the first injection (Week 4) and did not change the conclusions for this endpoint. The secondary immunogenicity endpoint was not recalculated by the statistician, using the revised PP population data but rather based on tabular data provided in the revised CSR submitted to CBER on 16 March 2016.

Results of the revised secondary endpoint analysis are presented in Table 5:

Table 5: Revised Secondary Immunogenicity Endpoint Analysis for Study DV2-HBV-10: SPR at Week 4 for Heplisav-B compared with Engerix-B for the Per-Protocol Analysis Population (Adults 18-55 years of age)

Visit	Heplisav-B[a] SPR (%) n/N	Engerix-B[b] SPR (%) n/N	Estimated Difference in SPR[c] (Engerix-B –Heplisav-B) (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
Week 4	23.5 % 354, 1502	4.1 % 19, 519	-19.5 (-22.2, -16.6)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.
[d] Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).
Source: *BLA 125248/0.42, DV2-HBV-10, Revised CSR, Table 11-2, page 279.*

Reviewer comment: *Similar to results of the primary immunogenicity endpoint, the SPR for Heplisav-B was non-inferior to that of the active comparator, Engerix-B, for the secondary immunogenicity endpoint, the SPR at four weeks after first vaccination, using the revised PP population. The net change in the number of subjects in the PP population in the revised secondary immunogenicity analysis had no significant effect numerically or statistically on this endpoint and did not change the conclusions of study DV2-HBV-10.*

6.1.11.3 Subpopulation Analyses

Re-analysis of immunogenicity using the revised PP population was restricted to the primary and secondary endpoint. Subgroup analyses were not performed.

Reviewer comment: *Given the negligible effect of the revised PP population on the primary and secondary immunogenicity endpoints, the revised PP population is not likely to have a significant effect on subgroup analyses of immunogenicity.*

6.1.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.1.10.1.3 Subject Disposition in this review, along with the prior discussion of subject dropouts/discontinuations in the clinical review for BLA STN 125428/0 dated 26 February 2013. Missing data were not imputed in this study.

6.1.11.5 Exploratory and Post Hoc Analyses

Study DV2-HBV-10 evaluated a number of exploratory endpoints, which comprised the SPR at Weeks 8, 12, 24, and 28 and the GMC at Weeks 4, 8, 12, 24, and 28 for both vaccine groups. An additional exploratory endpoint evaluated was the SPR at 4 weeks after the final active injection (Week 8 for Heplisav-B and Week 28 for Engerix-B).

Re-analysis of these exploratory endpoints using the revised PP population was performed by the Applicant and submitted in the CR received 16 March 2016.

These data (not presented) are summarized as follows:

- There was no significant numerical change in each respective exploratory endpoint.
- No statistically significant change in any of the exploratory endpoints was seen when compared to the original analysis.
- Conclusions regarding exploratory endpoints did not change with the revised PP population.

6.1.12 Safety Analyses

The safety analysis in study DV2-HBV-10 was not affected by the revised PP population and was previously reviewed by Dr. Lorie Smith under BLA STN 125428/0.

6.1.13 Study Summary and Conclusions

The Applicant included revised immunogenicity analyses in its March 2016 CR. Following a number of communications with the Applicant, including CBER's issuance of the November 2016 CR letter, and the Applicant's February 2017 CR, CBER was able to verify revised immunogenicity results. The revised PP population had no significant impact on the primary immunogenicity endpoint analysis or conclusion. The immune response to Heplisav-B was shown to be non-inferior to the immune response to Engerix-B. Applicant-initiated revisions of the PP population also had a negligible effect on the secondary immunogenicity endpoint, with no change in the overall conclusions of this study. The safety population was not affected by the change in the PP population. Therefore, please refer to the clinical review of the original submission regarding safety conclusions for study DV2-HBV-10.

6.2 Trial #2

An observer-blinded, randomized, parallel-group, multi-center phase 3 study comparing the safety and immunogenicity of Heplisav-B to Licensed Vaccine (Engerix-B) among Healthy Adults 40 to 70 years of Age (Protocol DV2-HBV-16; NCT01005407)

A revised CSR for study DV2-HBV-16 was submitted with the Applicant's CR (Complete Response) on 16 March 2016. Similar to study DV2-HBV-10, a revision to study DV2-HBV-16 was necessary to correct errors in the CSR (Clinical Study Report), which was submitted previously to the BLA in 2012. Please refer to Section 6.1 for details and related regulatory interactions, prior to CBER's issuance of a second CR letter in November 2016.

On 8 February 2017, in response to CBER's November 2016 CR letter, the Applicant submitted a CR to the CBER's three immunogenicity comments and included the requested corrected datasets, for verification of subject accounting of study DV2-HBV-16, and for verification of the primary immunogenicity analysis. The safety analysis for study DV2-HBV-16 was not impacted by the Applicant's responses to the CR letters.

6.2.1 Objectives

Briefly, the primary immunogenicity objectives of this phase 3 study were:

- To compare the proportion of subjects who exhibit a seroprotective immune response (SPR, defined as anti-HBsAg antibody levels greater than or equal to 10 mIU/mL) when measured at Week 12 following vaccination with Heplisav-B at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 32 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months.
- To demonstrate lot consistency for immune response as measured by the geometric mean concentration (GMC) at 4 weeks after the last active dose (Week 8) among three consecutively manufactured lots of Heplisav-B from the manufacturing process after minor modification.

The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with Heplisav-B when administered to subjects 40 to 70 years of age and to compare the safety profile to that of Engerix-B for this age group.

6.2.2 Design Overview

For the full clinical design overview of study DV2-HBV-16, please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013.

Briefly, one important difference in study design between studies DV2-HBV-16 and -10 was the time point used for comparing the SPR between Heplisav-B and Engerix-B (Week 32 vs. Week 28 for Engerix-B) for the primary immunogenicity analysis. This change in timing reflected the peak immunogenicity response for Engerix-B when compared to the peak immunogenicity time point for Heplisav-B (Week 12). Randomization in study DV-HBV-16 was 4:1 overall for Heplisav-B to Engerix-B (the allocation ratio of the three consistency lots to Engerix-B was 3:1), which differed from the 3:1 randomization of Heplisav-B to Engerix-B subjects in study DV-HBV-10.

6.2.3 Population
The study population for DV2-HBV-16 comprised hepatitis B seronegative male and female subjects who fulfilled essentially the same inclusion criteria as study DV2-HBV-10, with the exception that the allowed age range for this study was 40-70 years, rather than the 18- 55-year age range for study DV2-HBV-10.

6.2.4 Study Treatments or Agents Mandated by the Protocol
Subjects randomized to the Heplisav-B group received a total of two injections of Heplisav-B. Injections were administered at Week 0 and 4. Heplisav-B test product comprised 20 mcg recombinant HBsAg subtype *adw* with 3000 mcg 1018 adjuvant, manufactured by Rentschler BioTechnologie GmbH, Laupheim, Germany. The Heplisav-B lot numbers used in this study were TDG006, TDG008, TDG009, and TDG010.

Engerix-B (20 mcg HBsAg combined with 50 mcg alum adjuvant, GlaxoSmithKline Biologicals) was used as the active comparator in this study and dosed according to the manufacturer's instructions.

Placebo was 0.9% sterile saline for injection manufactured by Hospira, Inc. and was used as the third dose in the Heplisav-B arm.

6.2.5 Directions for Use
Each Heplisav-B injection was given intramuscularly (IM) into the deltoid muscle of either arm using a 1 to 1.5 inch, 25-gauge needle. The arm used for injection was alternated with each injection. Total injection volume was 0.5 mL to deliver 20 mcg of HBsAg and 3000 mcg of 1018. For the third injection at Week 24, Heplisav-B group subjects received placebo (0.9% sterile saline for injection), administered in 0.5 mL in the same manner as the 1018 HBsAg.

Subjects in the Engerix-B group received three IM injections, given as a 1.0 mL injection using a 25-gauge needle, at Week 0, 4, and 24.

6.2.6 Sites and Centers
This phase 3 study was conducted at 29 sites in the U.S. (25 investigators) and 3 sites in Canada (3 investigators). The principal investigator was Scott Halperin, M.D., Dalhousie University, Nova Scotia, Canada.

6.2.7 Surveillance/Monitoring
Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013 for a detailed Study Schedule.

Briefly, at study Week 0, and subsequently at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 44, and 52 (or early discontinuation) subjects returned to the study site to have blood drawn for quantitative measurement of anti-HBsAg concentrations and for evaluation of safety and tolerability. The immune response (anti-HBsAg) was measured using the (b) (4)

6.2.8 Endpoints and Criteria for Study Success
The primary immunogenicity endpoints (co-primary endpoints) of study DV2-HBV-16 were the following:

1. The between group difference SPR, as measured at Week 12 for Heplisav-B and Week 32 for Engerix-B. Heplisav-B

Success criteria for the non-inferiority comparison with Engerix-B was defined as the lower 2-sided 95% CI limit around Heplisav-B-B SPR – Engerix-B SPR > -10%.

2. Lot consistency in three consecutively manufactured lots of Heplisav-B from the manufacturing process after minor modification, measured by GMC at 4 weeks after the last active dose of Heplisav-B (Week 8).

Success criteria for the lot-to-lot consistency comparison was defined as follows: lot consistency was established in all three 95% CIs for the three pair-wise ratios of the GMCs from the consistency lots (TDG008, TDG009 and TDG010) were embedded in the interval between 0.667 and 1.5.

6.2.9 Statistical Considerations & Statistical Analysis Plan
For the statistical analysis plan of study DV2-HBV-16, please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2016 and statistical review dated 29 January 2013, respectively.

6.2.10.1 Populations Enrolled/Analyzed

Although three per protocol populations were used for the immunogenicity analysis in study DV2-HBV-16, only two of these were affected by the revised per protocol population during the 2015 audit of this study—(1) the noninferiority immunogenicity analysis and (2) the lot consistency immunogenicity analysis. The two per protocol populations affected by the revised analysis are defined as follows:

- Noninferiority Per Protocol Population: randomized subjects who received one of the three consistency lots of Heplisav-B or Engerix-B, received all three study injections as randomized and within the study visit windows, had no major protocol deviations, and had anti-HBsAg measurements and all injections within the specified day ranges.

- Lot Consistency Per Protocol Population: all subjects randomized to one of three consistency lots of Heplisav-B (TDG008, TDG009, and TDG010) who received the first two study injections within the study visit windows, had no major protocol deviations, and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.

In determining which subjects met criteria for inclusion into the noninferiority or lot consistency per protocol populations, major protocol deviations were defined as any of the following:

- Subject did not meet one or more enrollment criteria,
- Subject did not receive correct vaccine as randomized,
- Vaccine was given outside protocol-specified visit windows at the following visits: Noninferiority population--Weeks 4 or 24; lot consistency population--Week 4,
- Serum sample collection was obtained outside protocol-specified windows at the following visits: Noninferiority population--Weeks 12 or 32; lot consistency population--Week 8,
- Subject received prohibited concomitant medication(s) through the following visits: Noninferiority population--Week 32; lot consistency population--Week 8.

The immunogenicity analysis using the per-protocol population was considered primary.

Reviewer comment: *Re-analysis of study DV2-HBV-16 did not change the definitions of the non-inferiority and lot consistency per protocol populations but affected the number of subjects in each respective population. The same criteria for exclusion from the PP populations, as used in the original BLA submission, were used in the revised CSR of study DV2-HBV-16.*

6.2.10.1.1 Demographics
Demographic and baseline characteristics were similar between the two treatment groups, with no statistically significant differences found. The revised PP populations did not change any of the demographic variables except the number of subjects with baseline positive anti-HBs antibody—which changed very slightly for consistency lot TDG008 (decreased by one subject). Subject demographics are summarized in Table 6.

Reviewer Comment: *Subject demographics for study DV2-HBV-16 were fairly similar across treatment groups and between the Heplisav-B lots. Most subjects were hepatitis B seronegative Caucasians. The distribution of male and female subjects and subjects across the age strata was similar within each treatment group and between treatment groups, though there were slightly more subjects in the age strata 50-59 year. Revision in the PP populations, as shown in the revised CSR dated 16 March 2016, did not change subject demographics in any significant manner.*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Revisions to the PP population did not alter the medical/behavioral characterization of the enrolled population. Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0 dated 26 February 2016.

6.2.10.1.3 Subject Disposition
Similar to study DV2-HBV-10, a re-evaluation of study DV2-HBV-16 was performed by the Applicant, in order to address concerns identified by another regulatory agency in a related study. As a result of the Applicant's audit of DV2-HBV-16, a number of subjects were identified who were originally incorrectly included in the noninferiority and lot consistency PP populations. Also identified during this audit, were a subset of subjects who were incorrectly originally excluded from these respective PP analysis populations. Therefore, the Applicant submitted a revised CSR for study DV2-HBV-16 in the 16 March 2016 CR. Subject disposition data were verified by Excel spreadsheets and ADSL datasets provided in the 8 October 2016 partial IR response and 8 February 2017 CR.

A table of revised subject disposition for the noninferiority and lot consistency PP populations and subject accounting for the other study populations of DV2-HBV-16 is presented in Table 7 below.

Table 7: Revised Subject Disposition for Study DV2-HBV-16: Adults 40-70 years of age

Disposition	**Lot TDG008 (N=481)**	**Lot TDG009 (N=483)**	**Lot TDG010 (N=477)**	**Heplisav-B consistency Lots Total[a] (N=1441)**	**Lot TDG006 (N=528)**	**Engerix-B (n=483)**	**Total (n=2452)**
Screened							3793
Randomized	**481**	**483**	**477**	**1441**	**528**	**483**	**2452**
--Subjects enrolled in parallel with Lot TDG006	187 (38.9%)	183 (37.9%)	181 (37.9%)	551 (38.2%)	528 (100.0%)	185 (38.3%)	1264 (51.5%)
Safety Population	**481**	**481**	**477**	**1439**	**529[b]**	**481**	**2449**
--Subjects enrolled in parallel with Lot TDG006: Original	187 (38.9%)	182 (37.7%)	181 (37.9%)	550 (38.2%)	529 (100.0%)	185 (38.2%)	1264 (51.5%)
--Subjects enrolled in parallel with Lot TDG006: Revised	187 (38.9%)	182 (37.7%)	181 (37.9%)	550 (38.2%)	529 (100.0%)	184 (38.2%)	1263 (51.5%)
mITT Population	476 (99.0%)	478 (99.0%)	472 (99.0%)	1426 (99.0%)	521 (98.7%)	476 (98.6%)	2423 (98.8%)
--Subjects enrolled in parallel with Lot TDG006	186 (38.7%)	182 (37.7%)	178 (37.3%)	546 (37.9%)	521 (98.7%)	476 (98.6%)	2423 (98.8%)
Lot Consistency Per Protocol Population: Original Analysis	428 (89.0%)	438 (90.7%)	424 (88.9%)	1290 (89.5%)	455 (86.2%)	420 (87.0%)	2165 (88.3%)
Lot Consistency Per Protocol Population: Revised Analysis	423 (87.9%)	427 (88.4%)	414 (86.8%)	1264 (87.7%)	NA	NA	NA
Noninferiority Per Protocol Population: Original	366 (76.1%)	375 (77.6%)	382 (80.1%)	1123 (77.9%)	390 (73.9%)	359 (74.3%)	1872 (76.3%)
Noninferiority Per Protocol Population: Revised	366 (76.1%)	375 (77.6%)	380 (79.7%)	1121 (77.8%)	NA	NA	NA

Disposition	Lot TDG008 (N=481)	Lot TDG009 (N=483)	Lot TDG010 (N=477)	Heplisav-B consistency Lots Total[a] (N=1441)	Lot TDG006 (N=528)	Engerix-B (n=483)	Total (n=2452)
Bridging Study Population	165 (34.3%)	163 (33.7%)	158 (33.1%)	486 (33.7%)	446 (84.5%)	NA	NA
Completed Study	445 (92.5%)	444 (91.9%)	446 (93.5%)	1335 (92.6%)	483 (91.5%)	451 (93.4%)	2269 (92.5%)
Discontinued	36 (7.5%)	39 (8.1%)	31 (6.5%)	106 (7.4%)	45 (8.5%)	32 (6.6%)	183 (7.5%)
--Adverse Event	1 (0.2%)	0	0	1 (0.1%)	0	0	1 (0.0%)
--Subject Non-Compliance	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (0.3%)	1 (0.2%)	3 (0.6%)	9 (0.4%)
--Consent Withdrawn	9 (1.9%)	13 (2.7%)	8 (1.7%)	30 (2.1%)	15 (2.8%)	12 (2.5%)	57 (2.3%)
--Lost to Follow-up	17 (3.5%)	21 (4.3%)	15 (3.1%)	53 (3.7%)	28 (5.3%)	13 (2.7%)	94 (3.8%)
--Death	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
--Protocol Violation	1 (0.2%)	0	2 (0.4%)	3 (0.2%)	0	1 (0.2%)	4 (0.2%)
--Other	6 (1.2%)	3 (0.6%)	5 (1.0%)	14 (1.0%)	0	2 (0.4%)	16 (0.7%)

N= number of subjects randomized to the treatment group; mITT: Modified intent-to-treat; NA: Not applicable to PP Population.
[a] Lots TDG008, TDG009, and TDG010.
[b] In the safety population, subjects were grouped based on actual treatment received. Subject 47-707 was randomized to Engerix-B but received Heplisav-B lot TDF006 for injection 2 and was analyzed under Heplisav-B lot TDG006.
Source: *STN 125428/0, CSR, DV2-HBV-16, Section 10.2., Pages 65-66, STN 125428/0.42, Revised CSR, DV2-HBV-16, Section 10.2 Disposition of Subjects, Pages 296-297, STN 125428/0.66, Attachments 24c1-24c3,24c.6, pages 1-44, DV2-HBV-16 PP Merged Dataset in Excel (2012-2016), pages 1-987, STN 125428/0.72, Attachments 24c4-s4c6, pages, STN 125428/0.72, Module 1.11.3, Clinical Information Amendment.*

As a result of the reclassification of PP subjects, the net number of subjects excluded in the revised non-inferiority PP population reported was 8 (defined as: newly excluded subjects minus the newly included subjects) and the net number of subjects excluded in the revised lot consistency PP population was 26, according to the Applicant's revised CSR, 8 October 2016 partial IR response, and 8 February 2017 CR. Reclassification of subjects occurred on 15 September 2015, according to the 8 October 2016 partial IR Response and 8 February 2017 CR from the Applicant. Reclassification of the PP population did not affect the number of subjects who completed or who discontinued the study. Changes to the revised CSR as a result of the Applicant's audit slightly affected the noninferiority and lot consistency PP population numbers. The mITT and Safety population numbers remained unchanged.

Reviewer Comment: *The total proportion of subjects excluded from the revised PP population was small compared to the original PP population (generally < 2.0% for the two PP populations).*

Reasons for exclusion from the PP populations in the revised CSR of DV2-HBV-16 were (in decreasing order of frequency):

- Administration of vaccine not properly stored
- Subject not meeting enrollment criteria:
  - Pre-existing autoimmune disease
  - Anti-HBs level > 5.0 mIU/mL at baseline
- Subject did not receive correct vaccine as randomized
- Prohibited medication taken

Of the 21 Heplisav-B subjects who were previously excluded from the PP populations but included upon re-analysis, reasons for re-inclusion, according to the partial IR

Table 6: Summary of Demographic and Baseline Characteristics for Study DV2-HBV-16: Randomized Population: Adults; 40 – 70 years of age)

Characteristic	Lot TDG008 (N=481) n (%)	Lot TDG009 (N=483) n (%)	Lot TDG010 (N=477) n (%)	Heplisav-B consistency Lots Total[a] (N=1441) n (%)	Lot TDG006 (N=528) n (%)	Engerix-B (n=483) n (%)	Total (n=2452) n (%)
Age, years							
40-49	152 (31.6%)	153 (31.7%)	157 (32.9%)	462 (32.1%)	175 (33.1%)	160 (33.1%)	797 (32.5%)
50-59	193 (40.1%)	194 (40.2%)	189 (39.6%)	576 (40.0%)	208 (39.4%)	191 (39.5%)	975 (39.8%)
60-70	136 (28.3%)	136 (28.2%)	131 (27.5%)	403 (28.0%)	145 (27.5%)	132 (27.3%)	680 (27.7%)
N	481	483	477	1441	528	483	2452
Mean (SD)	54.1 (7.8)	54.1 (7.8)	53.9 (7.8)	54.0 (7.8)	54.1 (8.1)	53.8 (7.8)	54.0 (7.9)
Range	40-70	40-70	40-70	40-70	40-70	40-70	40-70
Gender							
Male	241 (50.1%)	229 (47.4%)	218 (45.7%)	688 (47.7%)	255 (48.3%)	237 (49.1%)	1180 (48.1%)
Female	240 (49.9%)	254 (52.6%)	259 (54.3%)	753 (52.3%)	273 (51.7%)	246 (50.9%)	1272 (51.9%)
Race							
White	400 (83.2%)	403 (83.4%)	389 (81.6%)	1192 (82.7%)	427 (80.9%)	402 (83.2%)	2021 (82.4%)
Black or African American	66 (13.7%)	72 (14.9%)	79 (16.6%)	217 (15.1%)	81 (15.3%)	68 (14.1%)	366 (14.9%)
Asian	4 (0.8%)	4 (0.8%)	6 (1.3%)	14 (1.0%)	12 (2.3%)	4 (0.8%)	30 (1.2%)
American Indian or Alaska Native	6 (1.2%)	1 (0.2%)	0	7 (0.5%)	4 (0.8%)	1 (0.2%)	12 (0.5%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.0%)
Other	5 (1.0%)	3 (0.6%)	2 (0.4%)	10 (0.7%)	4 (0.8%)	8 (1.7%)	22 (0.9%)
Ethnicity							
Hispanic	32 (6.7%)	28 (5.8%)	28 (5.9%)	88 (6.1%)	29 (5.5%)	33 (6.8%)	150 (6.1%)
Non-Hispanic	447 (93.3%)	455 (94.2%)	449 (94.1%)	1351 (93.9%)	499 (94.5%)	450 (93.2%)	2300 (93.9%)
Baseline Anti-HBs Antibody							
Positive[b]	8 (1.7%)	11 (2.3%)	10 (2.1%)	29 (2.0%)	19 (3.6%)	8 (1.7%)	56 (2.3%)

N= number of subjects randomized to the treatment group; SD = standard deviation
[a] Lots TDG008, TDG009, and TDG010.
[b] Seropositive to hepatitis B corresponds to antibody level ≥ 5 mIU/mL.
Source: *BLA STN 125428/0, CSR, DV2-HBV-16, Table 10-3, pages 69-70 of 215, BLA STN 125429/0.42, Revised CSR, DV2-HBV-16, Table 10-3, pages 303-305 of 480.*

Subjects were also categorized by weight, height, body mass index, and smoking status as exploratory variables (data not presented). No significant differences between the two treatment groups were seen for these characteristics. The majority of enrolled study subjects (79% for both treatment groups) were non-smokers, non-diabetic (90-92%), and non-obese (BMI ≤ 30 kg/m^2 56-57% for both treatment groups).

response dated 8 October 2017 and CR dated 8 February 2017 were generally due to error in protocol deviation assignment when in fact the subject had no protocol deviation (n=14). Less common reasons for re-inclusion included: not taking an exclusionary medication such as corticosteroids or taking corticosteroids within the allowed window (n=5), and change in exclusionary condition (n=2; subjects originally diagnosed with colon carcinoma did not have a malignancy but had benign colon adenoma).

Reviewer comment: *The reasons for excluding or including subjects in the revised PP populations were appropriate, given the Applicant's pre-specified criteria for inclusion into the noninferiority and lot consistency PP populations.*

CBER's review of the revised CSR for DV2-HBV-16 required verification of the net number of subjects excluded from the two affected PP populations (noninferiority and lot consistency). The clinical or the statistical reviewer were not able to verify subject disposition numbers for the revised noninferiority or lot consistency PP subjects, using the information provided in the revised CSR in the CR dated 16 March 2016. Despite a number of communications with the Applicant during the review cycle, including Information Requests (IRs) and teleconferences, persistent inconsistencies in the information submitted required re-evaluation and correction of the affected datasets by the Applicant before CBER could proceed with further review of these data. This resulted in issuance of an additional CR letter from CBER dated 10 November 2016, to request full accounting of the newly excluded or included per protocol subjects for this study, along with provision of a corrected analysis dataset subject level ADSL dataset that merged changes in the respective PP populations from the 2012 and 2016 ADSL datasets for study DV2-HBV-16.

In response to the November 2016 CBER CR request, the Applicant's CR dated 8 February 2017 contained detailed information for each per protocol subject that was 'newly excluded' or 'newly included' in the non-inferiority and lot consistency populations by referencing a partial IR response dated 8 October 2016 which contained this information. This information was provided in the form of Excel spreadsheets which tracked the change of subject disposition from the 2012 to 2016 CSR, along with provision of the merged ADSL dataset. Using the subject accounting data provided in the 8 October 2016 and 8 February 2017 submissions, the clinical review team verified the results for the revised per protocol populations, which were shown to be consistent, both numerically and in terms of tracking individual subjects for each PP population, with those provided in the revised CSR for DV2-HBV-16 dated 16 March 2016.

Reviewer comment: *Corrected datasets provided by the Applicant in the 8 October 2016 partial IR response and the 8 February 2017 CR, verified the subject numbers and disposition for the noninferiority and lot consistency per protocol populations. CR items 23 through 25 (immunogenicity) pertaining to subject accounting for study DV2-HBV-16 (also DV2-HBV-10) from CBER's CR letter dated 10 November 2016 were adequately addressed with the Applicant's 8 February 2017 response.*

6.2.11 Efficacy Analyses

Revised effectiveness analyses for study DV2-HBV-16 using the revised noninferiority and lot consistency populations were provided by the Applicant for the co-primary immunogenicity endpoints in the CR received 16 March 2016.

6.2.11.1 Analyses of Primary Endpoint(s)

Two primary immunogenicity endpoints were defined in study DV2-HBV-16. The first primary immunogenicity analysis was a comparison of the SPR at 8 weeks after the last active dose of study treatment between Heplisav-B (Week 12) and Engerix-B (Week 32), using the noninferiority per protocol population that combined the three Heplisav-B consistency lots (TDG008, TDG009, and TDG010; also referred to as the Heplisav-B group).

The lot consistency per protocol population was used for the co-primary immunogenicity endpoint of lot consistency of the immune response in subjects who received one of three Heplisav-B consistency lots.

The co-primary immunogenicity results were verified by the statistical reviewer, Dr. Xiang. Please refer to the statistical review from Dr. Xiang for further details regarding verification of the co-primary immunogenicity endpoints used the revised PP populations.

Table 8 presents the non-inferiority comparison of SPRs at 8 weeks after the last active dose of study treatment between Heplisav-B (Week 12) and Engerix-B (Week 32) for the revised per protocol population.

Table 8: Comparison of the SPR for Heplisav-B (Week 12) with Engerix-B (Week 32) for Study DV2-HBV-16 using the Revised Per-Protocol Analysis Population (Adults 40-70 years of age)

Visit	Heplisav-B[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Heplisav-B-Engerix-B) (95% CI)	Non-inferiority Criteria Met?[d] (Yes/No)
Week 12/ Week 32	90.1 % (1010/1121)	70.5 % (249/353)	19.6% (14.7%, 24.8%)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] Two-sided 95% CIs of the difference in seroprotection rates between the Heplisav-B group at 12 weeks and the Engerix-B group at 32 weeks was supported using the Newcombe score method with continuity correction.
[d] Non-inferiority was supported if the lower bound of the 2-sided 95% CI was > -10%.
Source: *STN 125428/0, CSR, DV2-HBV-16, Table 11-1, Page 83; STN 125428/0.42, Revised CSR, DV2-HBV-16, Table 11-1, Page 322.*

The SPR in the Heplisav-B group changed from 90.0% in the original immunogenicity analysis to 90.1% with the revised immunogenicity analysis (using the revised PP population). For the Engerix-B group, the SPR was unchanged from the original to revised immunogenicity analysis and was 70.5%. The estimated difference between these rates was unchanged at 19.6% (Heplisav-B- Engerix-B; 95% CI 14.7%, 24.7%). The upper bound of the 95% CI changed from 24.7% to 24.8% using the revised PP population.

Reviewer comment: *Because the lower limit of the 95% CI (14.7%) was greater than -10%, the SPR for the Heplisav-B group at Week 12 was non-inferior to the SPR for the Engerix-B group at Week 32 using the revised PP population for determination of the*

SPR. Criteria for demonstration noninferiority for this first co-primary immunogenicity endpoint was met using the revised, verified PP population and did not change this result numerically in any significant manner or change the study's conclusion with respect to this immunogenicity endpoint.

For the second co-primary endpoint of lot consistency of the immune response to consecutively manufactured lots of Heplisav-B, subjects were randomized to receive one of three consecutively manufactured lots (consistency lots): TDG008, TDG009, or TDG010. The primary endpoint for lot consistency of the immune response was based on the GMC at 4 weeks after the last active dose of Heplisav-B (Week 8) but was also measured at Week 12 because this time point was more clinically relevant (see original clinical review of BLA STN 125428/0, 26 February 2013).

The Applicant's revised GMC data from both Week 8 and Week 12, which corresponds to the revised primary immunogenicity endpoint for the lot consistency per protocol analysis, were analyzed and are presented in Table 9 below. This analysis presents comparisons of GMCs at 4 weeks (Week 8) and 8 weeks (Week 12) after the last active dose in subjects who received one of three Heplisav-B consistency lots.

Table 9: Comparison of the Anti-HBsAg Geometric Mean Concentrations (mIU/mL) among Heplisav-B Consistency Lots at Week 8 and Week 12 for Study DV2-HBV-16: Revised Lot Consistency Per Protocol Population; Adults 40-70 years of age

Visit	Lot TDG008 GMC (mIU/mL); 95% CI	Lot TDG009 GMC (mIU/mL); 95% CI	Lot TDG010 GMC (mIU/mL); 95% CI
Week 8[a]	36.1 (28.1, 46.4) N=428	32.1 (24.8, 41.5) N=427	39.8 (30.7, 51.5) N=414
Week 12[b]	80.3 (65.4, 98.5) N=420	81.2 (65.8, 100.2) N=424	89.0 (72.0, 109.9) N=412
	Adjusted GMC Ratio[a] (95% CI) Lot TDG008/Lot TDG009	**Adjusted GMC Ratio[a] (95% CI) Lot TDG010/Lot TDG008**	**Adjusted GMC Ratio[a] (95% CI) Lot TDG010/Lot TDG009**
Week 8[a]	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)
Week 12[b]	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)

CI = Confidence interval, GMC= geometric mean concentration, N = number of subjects with non-missing results in the analysis population in the treatment group. GMCs were adjusted for lot, center and age category.
[a] 4 weeks after the last dose of Heplisav-B.
[b] 8 weeks after the last dose of Heplisav-B.
Source: *STN 125428/0, CSR, DV2-HBV-16, Table 11-2, Page 85; STN 125428/0.42, Revised CSR, DV2-HBV-16, Table 11-2, Page 322.*

A re-analysis of lot consistency, using the revised and verified lot consistency population showed that at Week 8 (four weeks after the last active dose of Heplisav-B), the GMCs for the consistency lots changed from 35.3 to 36.1 mIU/mL for lot TDG008, from 34.1 to 32.1 mIU/mL for lot TDG009, and from 41.9 to 39.8 mIU/mL for lot TDG010 (original compared with revised GMCs). These numerical changes were negligible and did not change the 95% CI of the ratio of the GMCs for each lot comparison (i.e. lot TDG008/TDG009, lot TDG010/TDG008, and lot TDG010/TDG009).

At Week 12 (eight weeks after the last active dose of study vaccine), using the revised and verified PP population to calculate GMCs, the GMCs changed from 77.6 mIU/mL to 80.3 mIU/mL for lot TDG 008, from 82.9 mIU/mL to 81.2 mIU/mL for lot TDF 009, and from 90.5 mIU/mL to 89.0 mIU/mL for lot TDG010, respectively. The revised 95% CI of the pairwise ratios of the revised GMCs between the lots were entirely embedded within

the interval between 0.667 and 1.5. Clinical consistency of the three consecutively manufactured lots of Heplisav-B, as measured using the revised GMCs derived from the revised lot consistency PP population, was established at Week 12.

Reviewer comment: *The effect of the revised and verified PP population was negligible on the lot consistency analysis and did not change conclusions regarding this co-primary immunogenicity endpoint.*

Lot-to-lot consistency was demonstrated for the three consecutively manufactured lots, when compared at the most clinically relevant time point, which corresponded to that of the primary immunogenicity endpoint, i.e., measurement at 8 weeks after administration of the last dose of vaccine (Week 12 comparison).

Review of the two primary immunogenicity endpoints using the revised and verified noninferiority and lot consistency population demonstrated that Heplisav-B has a robust immune response and was non-inferior in its immune response to the chosen active comparator, Engerix-B. The Applicant fulfilled the criteria for success for the two co-primary endpoints using the revised PP populations.

6.2.11.2 Analyses of Secondary Endpoints

In addition to re-evaluation of the GMCs of the consecutively manufactured lots, revised SPRs based on the revised lot consistency PP population were also re-assessed as part of the determination of lot consistency and as a secondary immunogenicity endpoint.

Using the revised lot consistency PP population, the SPR analysis of the Heplisav-B consistency lots did not change numerically. At the pre-specified time point of 4 weeks after the last active dose of Heplisav-B (Week 8), the 95% CI for the pair-wise comparisons of the differences of SPRs between lot TDG008 and TDG009 (95% CI, -2.5%, 9.1%) and between TDG010 and TDG008 (95% CI, -4.5%, 6.8%) were embedded in the interval between -10% and 10% and therefore met the pre-specified lot consistency criterion. At Week 12 (8 weeks after the last active dose of Heplisav, also the time point for the primary immunogenicity endpoint), the 95% CIs of the pair-wise differences of the revised SPRs between the lots were entirely within the interval of -10% and 10%. Clinical consistency of the three consecutively manufactured lots of Heplisav-B, as measured by SPR, using the revised PP population, was established at Week 12. At all subsequent study visits (Weeks 18, 24, 28, 32, 36, 44, and 52); the 95% CIs of all of the three pair-wise comparisons of the differences of the revised SPRs were within the interval of -10.0% and 10.0% (data not shown).

Reviewer comment: *The revised lot consistency PP population did not numerically change the SPRs of the Heplisav-B consistency lots at Week 8 and 12. These data support a determination of lot consistency.*

6.2.11.3 Subpopulation Analyses

The Applicant performed unpowered subpopulation analysis using the revised non-inferiority PP population, in which the SPR of Heplisav-B was compared to Engerix-B. SPRs were re-analyzed by age (stratified by subjects 40-49 years of age, 50-59 years, and those 60-70 years) and by sex. These revised data were submitted in the CR received 16 March 2016 and demonstrated numerically similar results to those found for the original PP population. Stratification by age showed highest SPRs in the 40-49-year

age group. Slightly higher SPRs were seen in females than males, more commonly at the earlier time points in the study. Because these data were not powered to detect between group differences, they are not included, but summarized above.

Revised SPRs for the different age subgroups did not change numerically in any substantive manner and the majority of SPRs remained unchanged as a result of this re-analysis.

After Week 4, the SPR for both treatment groups were consistently highest in the age 40-49 year subgroup, followed by the 50-59 year subgroup. The SPR in the Heplisav-B group was higher than the Engerix-B group at all visits and for all age strata, and also appeared to increase more rapidly in the younger age group than in the oldest age group.

Reviewer Comment: *Conclusions regarding each age subgroup evaluated was unchanged as a result of the revised PP population, with the younger age groups showing a higher SPR.*

The revised sex subgroup analysis also remained largely unchanged, with no significant numerical difference for each analysis. The SPR difference between males and females in the Heplisav-B arm, at each study time point was small, and not significant. The re-analysis of SPR based on sex, did not change any conclusions regarding effectiveness of Heplisav-B (or Engerix-B).

Reviewer Comment: *Subgroup re-analysis by sex using the revised PP population revealed that both men and women responded similarly to Heplisav-B vaccination, though the SPR was generally slightly higher numerically in women than men. Based on the numerical differences seen, it is unlikely that these differences would be statistically or clinically significant.*

Because the majority of subjects were Caucasian and the original study was not adequately powered to detect significant changes in SPR based on racial and ethnic profiles, subgroup re-analyses by race or ethnicity was not conducted by the Applicant using the revised PP population.

Reviewer Comment: *In summary, subgroup analysis of Heplisav-B response based on age and sex did not reveal differences that were likely to have any clinical significance.*

6.2.11.4 Dropouts and/or Discontinuations

Dropouts and missing data were assumed to be missing completely at random. No imputations were made for missing data. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL.

For a complete discussion of handling of dropouts and missing data, please refer to the prior discussion of subject dropouts/discontinuations in the clinical review for BLA STN 125428/0 dated 26 February 2013.

6.2.11.5 Exploratory and Post Hoc Analyses

Although exploratory endpoints were evaluated by the Applicant in the original licensing application of Heplisav-B, a re-analysis of these exploratory endpoints using the revised PP population was not performed by the Applicant or submitted in the revised CSR, as part of the CR received 16 March 2016. Therefore, a re-analysis of exploratory endpoints is not included in this clinical review. Please refer to the clinical review of the original licensing application of Heplisav-B (BLA STN 125428/0) dated 26 February 2013 for a discussion of exploratory immunogenicity endpoints.

6.2.12 Safety Analyses

The safety analysis in study DV2-HBV-16 was not affected by the revised PP population and was previously reviewed by Dr. Lorie Smith under BLA STN 125428/0. Outstanding safety questions regarding the possible diagnosis of Tolosa-Hunt Syndrome in a subject who received Heplisav-B in study DV2-HBV-16, including results of solicited expert consultations regarding this diagnosis and possible relationship to Heplisav-B, are addressed in Section 5.4.2 of this review.

6.2.13 Study Summary and Conclusions

Review of the Applicant's revised immunogenicity data for the non-inferiority and lot consistency per protocol populations of study DV2-HBV-16 (the merged 2012 and 2016 versions), verified the accuracy of subjects allocated to each respective revised per protocol population. The Excel spreadsheets requested by CBER to track subjects' disposition status from the 2012 submission to the 2016 submission were provided by the Applicant and reviewed by the clinical reviewer. All subjects whose status was changed in the 2016 revised CSR were appropriately accounted for.

Furthermore, the Applicant's 8 February 2017 CR confirmed the accuracy of the co-primary immunogenicity endpoint analyses (non-inferiority comparison of Heplisav-B to Engerix-B and for Heplisav-B lot consistency) provided in the revised CSR for study DV2-HBV-16, submitted originally in the 6 March 2016 CR.

Review of the revised immunogenicity analyses for study DV2-HBV-16 using the revised and verified non-inferiority and lot consistency PP populations, failed to show any significant changes numerically or statistically for the two co-primary immunogenicity endpoints evaluated. As a result of the reclassification of PP subjects, the net number of subjects excluded in the revised non-inferiority PP population reported was 8 (defined as: newly excluded subjects minus the newly included subjects) and the net number of subjects excluded in the revised lot consistency PP population was 26. The net number of subjects excluded as part of this re-analysis represents a small proportion of the total number of subjects originally enrolled in both PP populations (approximately 2%). There was no impact of this change on the revised immunogenicity analysis.

In summary, the revised CSR for study DV2-HBV-16 demonstrated non-inferiority of Heplisav-B to an active comparator, Engerix-B (recombinant hepatitis B vaccine) and showed lot consistency for three lots of Heplisav-B.

6.3 Trial #3

DV2-HBV-23: "A Phase 3, Observer-Blinded, Randomized, Active-Controlled (Engerix-B), Multicenter Trial of the Safety and Immunogenicity of Heplisav-B™ in Adults 18 to 70 Years of Age; NCT 02117934)"

Study Initiation Date (first subject randomized): 18 April 18 2014
Study Completion Date (last subject last visit): 16 October 16 2015
Report Date: 1 March 2016

6.3.1 Objectives
The study objectives as stated by the Applicant are the following:

Primary Objectives

- To evaluate the overall safety of Heplisav-B with respect to clinically significant adverse events (AEs)
- To demonstrate the non-inferiority of the seroprotection rate (SPR, defined as the percentage of subjects with a serum concentration of antibodies to hepatitis B surface antigen [anti-HBs] ≥10 mIU/mL) induced by Heplisav-B compared with the SPR induced by Engerix-B at Week 28 in subjects with type 2 diabetes mellitus

Secondary Objectives

- To describe the frequency of new-onset granulomatosis with polyangiitis (GPA) and Tolosa-Hunt syndrome (THS) in Heplisav-B recipients and Engerix-B recipients
- To describe the frequency of new-onset thrombotic/thromboembolic AEs in Heplisav-B recipients and Engerix-B recipients
- To describe the frequency of new-onset abnormal thrombotic screens in Heplisav-B recipients and Engerix-B recipients
- To describe the frequency of new-onset laboratory abnormalities suggesting compromised renal function or renal injury in Heplisav-B recipients and Engerix-B recipients
- To demonstrate that the SPR at Week 28 induced by Heplisav-B is statistically significantly higher than the SPR induced by Engerix-B in subjects with type 2 diabetes mellitus, only if it is established that Heplisav-B is non-inferior to Engerix-B with regard to SPR at Week 28
- To demonstrate that the SPR at Week 24 induced by Heplisav-B is non-inferior to the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age, sex, body mass index (BMI), and smoking status
- To demonstrate that the SPR at Week 24 induced by Heplisav-B is statistically significantly higher than the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age group, sex, BMI, and smoking status, only if it is established that Heplisav-B is non-inferior to Engerix-B with regard to SPR

Reviewer comment: *Study DV2-HBV-23 was conducted in response to the November 2012 VRBPAC's decision that a larger safety database was needed to establish the safety of Heplisav-B. CBER advised the Applicant that immunogenicity had been established previously in studies DV2-HBV-10 and -16, and further that safety had not been established in the overall study population and thus the primary focus of study DV2-HBV-23 should be to establish safety in the entire, general study population and confirm effectiveness in this same population. The corresponding immunogenicity data are included in this review to confirm that the immunogenicity findings in study DV2-HBV-23 were consistent with those seen in studies DV2-HBV-10 and -16 and to*

determine that Heplisav-B was immunogenic in the population subgroups evaluated in DV2-HBV-23, including subjects with type 2 diabetes mellitus.

6.3.2 Design Overview
DV2-HBV-23 was a randomized, observer-blinded, active-controlled, multicenter, phase 3 trial in which eligible subjects were randomized in a 2:1 ratio to receive Heplisav-B or Engerix-B (approximately 5500 Heplisav-B subjects and 2750 Engerix-B subjects). At least 413 subjects with type 2 diabetes mellitus, defined as having a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin, were to be enrolled. Enrollment was stratified by site, age group (18 to 39, 40 to 70 years), and type 2 diabetes mellitus status. The Heplisav-B group received a 2-dose series of Heplisav-B at Weeks 0 and 4 and placebo at 24 weeks. The Engerix-B group received a 3-dose series of Engerix-B at 0, 4, and 24 weeks. Immunogenicity laboratory assessments were performed at Weeks 0, 24 and 28 and anti-HBsAg antibody level in Heplisav-B recipients at Week 24 (20 weeks following the second and final dose) was compared to anti-HBsAg antibody level in Engerix-B recipients at Week 28 (4 weeks following the third and final dose).

All subjects were monitored for safety by the collection of medically-attended adverse events (MAEs) reported as occurring through the completion of the trial (Week 56) or early discontinuation. All MAEs reported were further assessed by the investigator for meeting criteria for adverse events of special interest (AESI) and/or serious adverse events (SAEs). AESIs were pre-specified in a CBER-generated list of conditions considered by CBER to be potentially immune-mediated.

Reviewer comment: *Solicited adverse events and unsolicited adverse events not evaluated by medical personnel were not reported in DV2-HBV-23. For an analysis of these events reported in previous studies, please see the original BLA clinical review.*

A laboratory sub-study enrolling 300 subjects randomized 2:1 to receive Heplisav-B or Engerix-B at two participating sites was planned. This subset of subjects had blood and urine collected at pre-specified time points through Week 56 for safety laboratory assessments of renal function, coagulation, and antiphospholipid antibodies. Baseline assessment also included assessment of genetic factors predisposing subjects to coagulation abnormalities.

Reviewer comment: *In the previous studies, five subjects in the Heplisav-B group and no subjects in the Engerix-B group, reported pulmonary embolism following vaccination, including one fatal event in a male subject with no risk factors for thrombosis. Based on review of repeat dose toxicity studies, in which rats had interstitial nephritis following Heplisav-B, CBER requested that study DV2-HBV-23 incorporate assessment of renal function, including early markers of kidney injury, such as urine microalbumin/creatinine ratio.*

6.3.3 Population
Relevant eligibility criteria included:

- Adults 18 to 70 years of age, inclusive
- No previous receipt of any hepatitis B vaccine
- No history of hepatitis B or human immunodeficiency virus (HIV) infection or positive test for HBsAg, anti-HBs, antibody to hepatitis B core antigen (anti-HBc), or antibody to HIV

- No history of autoimmune disorder
- No medical condition considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments
- For the laboratory sub-study: History of venous thrombosis or pulmonary embolism or taking anticoagulants

Reviewer comment: *The Applicant stated that, in order to simulate the "real world" of vaccine delivery and in keeping with the intent of a large-scale phase 3 trial to closely mirror current medical care, DV2-HBV-23 enrollment was not limited to "healthy" adults. Therefore, enrollment exclusions were limited, and subjects with multiple comorbidities were eligible to enroll, including subjects with type 2 diabetes on oral or injectable hypoglycemic agent. Study DV2-HBV-10 excluded subjects with clinically debilitating disease and in DV2-HBV-16, the inclusion criteria contained a statement that enrolled subjects should be healthy. Study DV2-HBV-23's eligibility criteria did not contain such a statement, although Section 4.1.3 of the protocol stated the population was to be healthy. Based upon baseline medical conditions, the Applicant did enroll a population that had more chronic medical conditions as compared to prior studies.*

6.3.4 Study Treatments or Agents Mandated by the Protocol
Heplisav-B: Each 0.5 mL dose contains 20 mcg of recombinant HBsAg subtype *adw* produced in *Hansenula polymorpha* yeast cells and 3000 mcg of 1018 phosphorothioate oligodeoxynucleotide adjuvant formulated in an 8 mM sodium phosphate/154 mM sodium chloride/ 0.01% w/w polysorbate 80/pH 7.0 buffer. The placebo was a 0.5 mL commercially available preservative-free, normal saline for injection (Sodium Chloride Injection, USP, 0.9%).

The study included a control group in which subjects were administered a 1 mL dose of Engerix-B, a licensed HBV vaccine, manufactured by GlaxoSmithKline.[24] Please see the Engerix-B Package Insert for product information.

Subjects were randomly assigned in a 2:1 ratio to receive Heplisav-B or Engerix-B. Unblinded study personnel used an interactive voice and web response system (b) (4) to obtain a subject number and vial number for each subject.

The subjects and the study personnel conducting clinical safety evaluations were blinded to treatment assignment, with subjects receiving normal saline placebo as the third dose. Study drug was not packaged or labeled in a blinded manner; therefore, designated study site personnel with no other study responsibilities were unblinded so they could prepare and/or administer the study injections. An unblinded study monitor with no other study responsibilities confirmed drug accountability. Unblinded staff was not involved in assessing safety events and were instructed not to communicate treatment assignments to the personnel responsible for assessing safety.

Reviewer comment: *The planned randomization was deemed adequate by the statistical reviewer. In review of a draft protocol of this study under IND 12692, regarding blinding procedures, CBER noted the Applicant's proposal to prevent subjects from knowing whether they were receiving 0.5 mL of candidate vaccine or 1.0 mL of Engerix-B by having subjects turn their heads away when vaccinated. CBER raised concerns about potential for unblinding and requested that the Applicant provide the rationale for concluding that this approach would maintain the study blind, or propose another means of blinding subjects to treatment. The Applicant's rationale was that the*

difference in volumes was unlikely to be perceived by a subject during injection and that the method of blinding subjects was similar to that used in previous studies, including studies DV2-HBV-10 and -16. In addition to the subjects themselves, the investigator and study staff evaluating the subjects were to remain unaware of the treatment assignment. Based on the reasons stated in the review of DV2-HBV-10 and -16 in the initial BLA submission, this observer-blind approach for DV2-HBV-23 was also deemed appropriate.

6.3.5 Directions for Use
Each 0.5 mL dose of Heplisav-B or placebo and each 1 mL dose of Engerix-B was to be administered into the deltoid muscle.

6.3.6 Sites and Centers
This study was conducted by 40 investigators at 40 centers, all in the United States (U.S.). The study sites and investigators are provided in Table 10 below.

Table 10. Participating clinical sites with number of subjects enrolled by study group into the Safety Population, Study DV2-HBV-23

Site #	Location	Heplisav-B Group n	Heplisav-B Group %	Engerix-B Group n	Engerix-B Group %	Total n	Total %
101	Murray, UT	58	2.1%	118	2.1%	176	2.10%
102	Aurora, CO	46	1.7%	92	1.6%	138	1.65%
103	Mesa, AZ	63	2.3%	125	2.2%	188	2.25%
104	Henderson, NV	52	1.9%	106	1.9%	158	1.89%
105	Chandler, AZ	99	3.6%	198	3.5%	297	3.55%
106	Greer, SC	104	3.7%	207	3.7%	311	3.72%
107	Tempe, AZ	69	2.5%	135	2.4%	204	2.44%
108	Elkhorn, NE	33	1.2%	71	1.3%	104	1.24%
109	Phoenix, AZ	62	2.2%	127	2.3%	189	2.26%
110	Anderson, SC	36	1.3%	74	1.3%	110	1.31%
111	Plano, TX	23	0.8%	47	0.8%	70	0.84%
112	Glendale, AZ	91	3.3%	183	3.3%	274	3.27%
113	Vista, CA	41	1.5%	79	1.4%	120	1.43%
114	Santa Rosa, CA	46	1.7%	92	1.6%	138	1.65%
115	Evansville, IN	49	1.8%	100	1.8%	149	1.78%
116	San Antonio, TX	85	3.1%	172	3.1%	257	3.07%
117	Centennial, CO	35	1.3%	72	1.3%	107	1.28%
118	Council Bluffs, IA	64	2.3%	129	2.3%	193	2.31%
119	Birmingham, AL	73	2.6%	145	2.6%	218	2.61%
120	Anderson, SC	113	4.1%	227	4.1%	340	4.06%
121	Tucson, AZ	52	1.9%	107	1.9%	159	1.90%
122	Chicago, IL*	197	7.1%	389	7.0%	586	7.00%
123	Phoenix, AZ	35	1.3%	67	1.2%	102	1.22%
124	Las Vegas, NV	45	1.6%	90	1.6%	135	1.61%
125	Pinellas Park, FL	109	3.9%	218	3.9%	327	3.91%
126	Cincinnati, OH	82	2.9%	170	3.0%	252	3.01%
128	Edina, MN	57	2.0%	114	2.0%	171	2.04%
129	Dallas, TX	94	3.4%	189	3.4%	283	3.38%
130	Akron, OH	105	3.8%	206	3.7%	311	3.72%

Site #	Location	Heplisav-B Group n	Heplisav-B Group %	Engerix-B Group n	Engerix-B Group %	Total n	Total %
131	Phoenix, AZ	78	2.8%	161	2.9%	239	2.86%
132	Columbus, OH	60	2.2%	117	2.1%	177	2.12%
133	Chandler, AZ	56	2.0%	111	2.0%	167	2.00%
134	Mesa, AZ	105	3.8%	206	3.7%	311	3.72%
135	Colorado Springs, CO	86	3.1%	166	3.0%	252	3.01%
136	Scottsdale, AZ	66	2.4%	137	2.5%	203	2.43%
137	St. Louis, MO	42	1.5%	89	1.6%	131	1.57%
138	Atlanta, GA	62	2.2%	131	2.3%	193	2.31%
139	Fremont, NE	76	2.7%	156	2.8%	232	2.77%
140	Omaha, NE	50	1.8%	101	1.8%	151	1.80%
141	Chandler, AZ	37	1.3%	75	1.3%	112	1.34%
222	Chicago, IL*	45	1.6%	88	1.6%	133	1.59%

Source: Adapted from - BLA 125428/0.42, Module 5.3.5.1, CSR DV2-HBV-23, Appendix 16.1.4
Total proportions may not add up to 100% due to rounding of proportions at individual sites.
* Sites 122 and 222 were the same site under the same investigator, but were assigned two site numbers due to the number of subjects screened.
n = number of subjects

The Applicant provided a list of twenty-four subjects who transferred sites during the study. These subjects were analyzed by the center at which they were originally enrolled and randomized. In 125428/0.74, in response to a CR item, the Applicant clarified that subjects were allowed to transfer to another study site once, if they relocated to another city.

Reviewer comment: *The site in Chicago, IL (122 and 222) enrolled more subjects than any other site. The remaining sites enrolled a median of 2.25% of the total vaccinated cohort. Subjects who transferred sites represented a small number of subjects of the total vaccinated cohort and are unlikely to significantly impact immunogenicity outcomes. However, to evaluate whether handling of transferred subjects influenced or reflected the quality of study conduct and data monitoring, the Applicant was asked in the November 2016 CR letter (item 30) to clarify the reasons for transfer and procedures for following these subjects. The procedures for transitioning subjects appeared adequate.*

6.3.7 Surveillance/Monitoring

Subjects participated in a screening period up to four weeks prior to first dose and could be rescreened one time if they had equivocal laboratory results or if they were unable to receive vaccination during the screening window. MAEs, SAEs, and AESIs were monitored through Week 56, one year after the last dose of Heplisav-B and 7 months after the last dose of Engerix-B. Subjects completed study-specific assessments through clinic visits scheduled at Weeks 0, 4, 24, 28, and 56 and through completion of an internet questionnaire about health care encounters at Weeks 8, 40, and 52. Subjects who reported a medically attended adverse event (MAE) were contacted by telephone to provide relevant information. Otherwise, over the course of the trial, all subjects received a monthly reminder by text message or email to answer questions about health care encounters immediately after they happened.

Reviewer comment: *Subjects in the Heplisav-B and Engerix-B groups were monitored for the same total length of time. However, differences in dose and schedule must be accounted for when assessing AEs based on time following vaccination, as Engerix-B*

subjects will have more observation time when examining AEs reported in a discrete time interval following vaccination, and will have very little observation time greater than 6 months following the last active dose.

In most subjects, immunogenicity assessments, but no safety laboratory assessments, were conducted. In the laboratory sub-study, a subset of subjects had blood and urine collected at Weeks 0, 4, 8, 24, and 56 for the following safety assessments: renal function (blood chemistry, creatinine, complete blood count with differential, urine microalbumin, and urinalysis including microscopic), clotting (prothrombin time, partial thromboplastin time), and antiphospholipid antibodies (lupus anticoagulant; anti-cardiolipin immunoglobulin [Ig]G and IgM; and anti-beta2 glycoprotein 1 IgG and IgM). In addition, at Week 0, blood was collected for Protein C, Protein S, antithrombin 3, and genetic testing for factor V Leiden deficiency. Only clinically significant laboratory abnormalities, as determined by the investigator, were to be recorded as MAEs.

Use of any medication during the 28 days prior to first injection through Week 56 or the early discontinuation visit was solicited from each subject and recorded in source documents. However, in the CRF, all concomitant medications through 4 weeks after the last study injection (Week 28) were recorded. After Week 28, only the following medications were entered in the CRF: immunosuppressive medications; immunoglobulins; blood products; vaccines; any medications, including over-the-counter medications, administered for treatment of a MAE, AESI, AIAE, or SAE; and any prohibited medication pre-specified in the protocol.

Reviewer comment: *Concomitant medication monitoring for approximately six months following vaccination may not assist in capturing some immune-mediated events that may follow an indolent course and/or require an extended period of time prior to diagnosis.*

Subjects who reported MAEs that were assessed by the investigator as potential AESIs were referred to an appropriate specialist for assessment. Regardless of the assessment of the specialist, the MAE was subsequently reviewed by an independent Safety Evaluation and Adjudication Committee (SEAC). The SEAC was a blinded committee comprised of two experts in autoimmune diseases and one infectious disease physician, all external to the Applicant and not otherwise involved in the study. The SEAC was responsible for reviewing clinical information on all potential AESIs to determine if the event was autoimmune in etiology. If the event was determined to be autoimmune, the SEAC assessed whether the event was pre-existing or new-onset and whether the event was related to treatment based on a > 50% probability. The SEAC provided adjudication results to the Applicant or its designee and these results were provided to CBER and the DSMB. For selected subjects with a potential autoimmune disorder, autoantibody testing was performed by the central laboratory on selected stored serum samples (typically the Week 0 sample) to determine if the event was autoimmune and pre-existing or new-onset.

Reviewer comment: *This process in study DV2-HBV-23 differed from that of DV2-HBV-16 in that in study DV2-HBV-16, potential AESIs were referred to a specialist and only events that were assessed by the specialist as autoimmune adverse events were referred to the SEAC for adjudication. This likely contributed to the increase in SEAC-reviewed events in DV2-HBV-23 compared to -16. CBER reviewed the SEAC charter under IND 12692, as well as the revised SEAC charter and found the revised charter*

acceptable. As the SEAC Chair had presented for the Applicant at the VRBPAC meeting, CBER requested that the Applicant submit financial disclosure information for the Chair, as well as the other two members of the SEAC. In response, the Applicant submitted financial disclosure information for the SEAC members in which all three members declared no financial interest.

AIAEs were defined as MAEs not included in the list of AESIs but adjudicated as autoimmune by the SEAC. As no AIAEs were identified in study DV2-HBV-23, they are not further discussed. As per the protocol and SEAC Charter, only events that were determined by the SEAC to be autoimmune required the SEAC to assess whether the event was new-onset and related to vaccination. The AESI list includes conditions that were not considered autoimmune by the SEAC but may be immune-mediated (for example, Bell's palsy). The SEAC was not required to assess these events for onset or relationship to vaccination.

For subjects who reported a venous thrombotic/thromboembolic event (VTE), such as a deep vein thrombosis (DVT), superficial thrombophlebitis, or pulmonary embolus (PE), the protocol specified additional evaluations. Risk factors predisposing the subject to thrombotic events were collected and subjects were to return to the study site to have the following blood tests performed: Protein C, Protein S, antithrombin 3, genetic test for factor V Leiden deficiency, and antiphospholipid antibodies (lupus anticoagulant; anti-cardiolipin IgG and IgM; and anti-beta2 glycoprotein 1 IgG and IgM). If these samples could not be obtained, stored blood was to be tested for antiphospholipid antibodies. Please see Section 6.3.12.2 for a discussion of thrombophilia testing in subjects with VTE.

The study was conducted under the supervision of a DSMB, which was composed of an infectious disease physician, an autoimmune disease expert, and a statistician that was external to the Applicant and were not otherwise involved in the study. The DSMB performed three pre–specified reviews.

Reviewer comment: *The DSMB convened an additional ad-hoc meeting, at the request of the Applicant, to review three myocardial infarctions and two deaths that occurred early in the trial (one MI occurred prior to vaccination). The recommendation after this ad-hoc meeting was to submit all fatal reports and cardiac SAEs to the DSMB on a regular basis throughout the trial, but no changes to the protocol were advised by the DSMB. The meeting minutes from each open session, but not closed session, were submitted to CBER following each meeting.*

The Applicant used a contract research organization, (b) (4), for monitoring study procedure compliance and for data management. Study sites were monitored by (b) (4) according to GCP.

6.3.8 Endpoints and Criteria for Study Success
Primary Endpoints

- Proportion of subjects with new-onset MAEs
- Proportion of subjects with new-onset SAEs or deaths
- Proportion of subjects with new-onset AESIs
- Proportion of subjects with new-onset AESIs + AIAEs
- SPR at Week 28 in subjects with type 2 diabetes mellitus

Secondary Endpoints

- Proportion of subjects with new-onset GPA or THS
- Proportion of subjects with new-onset thrombotic events
- Proportion of subjects with new-onset abnormal thrombotic screens in the laboratory sub-study
- Proportion of subjects with new-onset abnormal renal blood or urine tests in the laboratory sub-study
- SPR at Week 24 in Heplisav-B subjects and at Week 28 in Engerix-B subjects

For the primary immunogenicity endpoint, Heplisav-B was considered to be non-inferior to Engerix-B if the lower limit of the 95% confidence interval (CI) of the difference in SPRs (Heplisav-B minus Engerix-B SPR) was greater than -10%. This analysis was based on the PP population. Type 2 diabetic subjects were defined as having a clinical diagnosis of type 2 diabetes and taking an oral or non-insulin injectable hypoglycemic agent(s) and/or insulin. The methodology(ies) by which the clinical diagnosis of type 2 diabetes was ascertained was not defined in the clinical protocol or discussed in the CSR for DV2-HBV-23, but presumably would have been based on clinical presentation and laboratory testing. Hemoglobin A1c (HbA1c) levels (an indication of the degree of glucose control) were obtained at Visit 0 (baseline) and Visit 24 on all subjects with a diagnosis of type 2 diabetes mellitus.

Reviewer comment: *Diabetic subjects enrolled in DV2-HBV-23 were determined by the investigator to have a diagnosis of type 2 diabetes prior to study enrollment and to be taking an appropriate hypoglycemic agent at the time of enrollment. Study design of DV2-HBV-23 also included determination of baseline HbA1c levels, with follow-up at Week 24 – an appropriate measurement to assess the extent of glucose control in this population.*

The clinical reviewer deems the protocol-specified methods used in subjects to determine type 2 diabetes acceptable and consistent with the practice of medicine.

For the secondary immunogenicity endpoints, Heplisav-B was considered to be non-inferior to Engerix-B if the lower limit of the 95% confidence interval (CI) of the difference in SPRs (Heplisav-B minus Engerix-B SPR) was greater than -10%. This analysis was based on the PP population.

Reviewer comment: *The statistical criteria for determination of non-inferiority between Heplisav-B and Engerix-B were the same for the primary and secondary immunogenicity endpoints. The Week 24 vs. Week 28 time points for the secondary endpoints for Heplisav-B and Engerix-B, respectively, were chosen for comparison because previous phase 3 studies showed that the Heplisav-B SPR peaked at Week 24 and the Engerix-B SPR peaked at Week 28.*

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations

Agreement regarding the number of subjects enrolled followed a number of discussions with CBER regarding the need to increase the size of the total safety database for this product. The sample size of the trial was estimated to be approximately 8250 subjects,

which included approximately 5500 Heplisav-B subjects and 2750 Engerix-B subjects. Assuming a 10% non-completion rate, this sample size was expected to provide approximately 5000 Heplisav-B subjects and 2500 Engerix-B subjects available to be evaluated at Week 56. Subjects who discontinued the study early were not replaced.

The Applicant provided an analysis of the probabilities of identifying certain AESIs in a study of 5000 Heplisav-B recipients. They estimated the rate of AESIs plus AIAEs as reported in the Heplisav-B safety database prior to DV2-HBV-23 was 300/100,000. They concluded that with 5000 Heplisav-B recipients, they would expect 15 new-onset autoimmune disorders in the Heplisav-B group, which would rule out an incidence greater than 0.49% with a type I error rate of 5%.

Reviewer comment: *The Applicant estimated their expected rate of AESIs based upon their previous Heplisav-B database, which the reviewer does not think would provide an accurate estimate of background incidence of autoimmune disease for the following reasons:*

- *If the increased rate of AESIs noted in previous trials with Heplisav-B were causally related to Heplisav-B exposure, then using the clinical trial population to calculate the background incidence of the event of interest would falsely overestimate the rate of that event.*
- *Different studies used different methods for determining whether events were autoimmune.*
- *It is not clear that the populations of prior studies and study DV2-HBV-23 would be expected to have the same risk of autoimmune disease.*
- *The estimate also groups all AESIs and is therefore an over-estimate of any individual autoimmune disease.*

For these reasons, a true baseline of all AESIs is much more complicated to estimate and thus, a comparison of reported events between groups is likely to provide more information.

The Applicant calculated that a disease with a 0.02% incidence rate could be expected to occur in one subject in a study of 5000 subjects, yielding a 95% CI of 0%, 0.1%. With respect to rare immune-mediated diseases, such as the GPA and THS that were reported in the previous studies, they noted that if the true incidence of these diseases following vaccination is 2/4425, there would be a 90% chance that at least one case of GPA or THS would occur among a study of 5000 Heplisav-B recipients. The Applicant noted that a population-based incidence of GPA in the United States has not been reported. In one population-based study, the prevalence of GPA has been reported to be 3 per 100,000 (1:33,000).[25] The Applicant's analysis of National Hospital Discharge Survey data from 2005 to 2009 found an incidence of GPA of 1.5 per 100,000. Thus, they estimate the incidence of GPA to be between 1.5 and 3 per 100,000 (average is 2.25 per 100,000). Using the average estimated incidence, they calculated an 11% probability that at least one event with a rate of 1 in 44,000 would occur among these 5000 Heplisav-B subjects. If the background incidence of these events is 1 in 44,000, they estimated the probability that at least two such events would occur in 5000 subjects is 0.6%.

Reviewer comment*: The sample size necessary to definitively rule out an association between an investigational product and a rare disease is prohibitive in a pre-licensure study.*

Demographics
Descriptive statistics were used to summarize demographic and other baseline characteristics.

Immunogenicity Assessments
The per protocol population was the primary analysis population for all immunogenicity analyses. Both Week 24, and Week 28 SPR and geometric mean concentration (GMC), as well as (95%) confidence limits, were computed in Heplisav-B and Engerix-B subjects as secondary immunogenicity endpoints and as a primary immunogenicity endpoint in the subset of subjects defined as having type 2 diabetes mellitus. Additional sensitivity analyses were performed to account for factors such as diabetes severity, duration, and control. No imputations were made for missing data for the immunogenicity analysis.

Safety Assessments
All safety data were analyzed descriptively and analyses were based on the Safety Population. Summary descriptive statistics were used to describe the incidence of MAEs, AESIs, AESIs plus AIAEs, SAEs, and deaths reported through the Week 56 visit. Incidence of new-onset VTE AEs was also summarized by treatment group. The number and percentage of subjects reporting specific concomitant medications and non-study vaccinations during the specified study period were summarized by treatment group.

Reviewer comment: *The protocol specified that 95% confidence interval for MAEs, AESIs, AESIs plus AIAEs, SAEs, and deaths could have been constructed by treatment group and, when appropriate, a measure of relative risk between treatment groups could be estimated. However, the Applicant did not provide these analyses as they "decided they were not necessary."*

Changes from baseline laboratory results were summarized at each study visit for each treatment group and shift tables were provided. The proportion of subjects with abnormal test results was summarized by treatment group. Abnormal test results were determined based on the central laboratory reference standards. The Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials was used for grading the severity of laboratory abnormalities.

6.3.10 Study Population and Disposition
A total of 12,207 subjects were screened. Of subjects screened, 3,883 (32%) were screen failures. In Amendment 125428/0.54, in response to an IR sent on 28 June 2016, the Applicant submitted an additional dataset containing reasons for screen failure. Reasons for screen failure as determined by the reviewer-generated analysis of that dataset appear in the table below.

Table 11. Reviewer-generated analysis of reasons for screen failure, screened population, DV2-HBV-23

Reason	n	%
History of hepatitis B or HIV infection or positive test for HBsAg, anti-HBs, anti-HBc, or antibody to HIV	2513	65.6
Other medical condition	434	11.3
Able to comprehend and availability for all required study procedures	339	8.8
History of autoimmune disorder	289	7.5
Previous receipt of hepatitis B vaccine	103	2.7
Able and willing to provide informed consent	70	1.8
Received prohibited medication within 28 days: any vaccine, systemic corticosteroids > 3 consecutive days, other immunomodulators or immune suppressive medication, G-CSF, GM-CSF, or any other investigational medicinal agent	48	1.3
Diagnosis of cancer within the last 5 years, undergoing chemotherapy, or expected to receive chemotherapy	36	0.9
If female, subject is pregnant, nursing, or planning to become pregnant during the trial period	16	0.4
History of venous thrombosis, pulmonary embolism, or taking anticoagulants	12	0.3
History of sensitivity to any component of study vaccines	7	0.2
Woman of childbearing potential not consistently using an acceptable method of contraception or abstinence through Week 28	5	0.1

Source: BLA 125428/0.54, Module 5.3.5.1, Reviewer-generated analysis from dataset ADSF
n = number of subjects with inclusion or exclusion criteria
Total % does not equal 100% because subjects may have multiple reasons for screen failure.

Reviewer comment: *A majority of subjects were screen failures due most likely to prior HBV vaccination, or to prior HBV infection or HIV infection. The proportion of subjects who failed screening and the primary reasons for screen failure are not unlike other similarly designed vaccine trials.*

Six subjects were randomized but not treated, five subjects randomized to Heplisav-B and one subject randomized to Engerix-B. The reasons for study discontinuation of these six subjects were consent withdrawn (three subjects randomized to Heplisav-B, one subject randomized to Engerix-B) and physician decision (two subjects randomized to Heplisav-B).

Reviewer comment: *The number of subjects who discontinued following randomization and prior to treatment is small and would have been unlikely to significantly impact the immunogenicity outcomes.*

6.3.10.1 Populations Enrolled/Analyzed

The Per Protocol (PP) population was defined as: all randomized subjects who received all study injections, had no major protocol deviations, and had anti-HBs levels obtained within the protocol-defined study visit window at Week 28. The PP population was the primary analysis populations for all immunogenicity analyses.

The modified Intent-To-Treat (mITT) population was defined as: all randomized subjects who received at least one study injection and had at least one post-injection

immunogenicity evaluation. The mITT population was used for supportive and confirmatory immunogenicity analyses.

The Safety Population (SP) was defined as: all subjects who received at least one injection of study drug, excluding subjects who had no on-study safety data. All subjects treated were included in the SP. The SP population was the primary analysis populations for all safety analyses.

6.3.10.1.1 Demographics

The table below shows the demographic characteristics in the SP in study DV2-HBV-23.

Table 12. Demographics for the Safety Population, Study DV2-HBV-23

Demographic	Category	Heplisav-B n = 5587	Engerix-B n = 2781	Total n = 8368
Age	Mean (SD)	50.36 (11.74)	50.37 (11.68)	50.37 (11.72)
	Median	52	52	52
	Minimum	18	18	18
	Maximum	71	70	71
Age	18 – 29 years	260 (4.7%)	131 (4.7%)	391 (4.7%)
	30 – 39 years	872 (15.6%)	430 (15.5%)	1302 (15.6%)
	40 – 49 years	1269 (22.7%)	632 (22.7%)	1901 (22.7%)
	50 – 59 years	1765 (31.6%)	895 (32.2%)	2660 (31.8%)
	≥ 60 years	1421 (25.4%)	693 (24.9%)	2114 (25.3%)
Gender	Male	2844 (50.9%)	1391 (50.0%)	4235 (50.6%)
	Female	2743 (49.1%)	1390 (50.0%)	4133 (49.4%)
Race	White	3968 (71.0%)	2007 (72.2%)	5975 (71.4%)
	Black or African American	1461 (26.1%)	696 (25.0%)	2157 (25.8%)
	Asian	57 (1.0%)	38 (1.4%)	95 (1.1%)
	American Indian or Alaska Native	60 (1.1%)	24 (0.9%)	84 (1.0%)
	Native Hawaiian or Other Pacific Islander	14 (0.3%)	7 (0.3%)	21 (0.3%)
	Other	25 (0.4%)	9 (0.3%)	34 (0.4%)
	Unknown	2 (0.0%)	0 (0.0%)	2 (0.0%)
Ethnicity	Hispanic or Latino	521 (9.3%)	239 (8.6%)	760 (9.1%)
	Not Hispanic or Latino	5062 (90.6%)	2541 (91.4%)	7603 (90.9%)
	Unknown	4 (0.1%)	1 (0.0%)	5 (0.1%)

Source: Adapted from - BLA 125428/0.42; Module 5.3.5.1, CSR DV2-HBV-23, Table 10-5, p.60
SD = standard deviation

Subjects vaccinated had a mean age of 50.4 years and were 50.6% male; 71.4% White, 25.8% Black, 1.1% Asian, 1.0% American Indian or Alaska Native; 90.9% not Hispanic, and 9.1% Hispanic. In the Heplisav-B group, there were slightly higher proportions of men (50.9% Heplisav-B, 50.0% Engerix-B) and Hispanics (9.3% Heplisav-B, 8.6% Engerix-B), and a slightly lower proportion of Asians (1.0% Heplisav-B, 1.4% Engerix-B) compared with the Engerix-B Group.

Reviewer comment: *Study groups had similar demographics in the safety population and any differences are small and unlikely to impact the outcomes in a clinically significant way. Based on the discussion during the VRBPAC Meeting on 15 November 2012, some Advisory Committee members recommended that the Applicant pursue enrollment of a more diverse study population and enroll greater numbers of certain groups, such as Asians. Asians did not make up a large subpopulation in study DV2-HBV-23; however, enrollment of Black or African American subjects was higher than for studies DV2-HBV-10 or -16 (2% and 15%, respectively).*

Subject demographics for the PP population were similar to that of the safety population and summarized in Table 14.1.2.1.3 of the CSR for DV2-HBV-23. There were no significant differences between these two populations that would have impacted interpretation of safety or effectiveness. One of the enrolled subjects excluded from the PP population was a 71-year old male subject assigned to the Heplisav-B group. The two study groups in the PP population had similar proportions of male subjects.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The Applicant presents an analysis of baseline medical and behavioral characteristics of the subjects in DV2-HBV-23 in the CSR and the Clinical Summary of Safety (CSS). Most subjects reported at least one medical condition: 91.8% of subjects in the Heplisav-B and 91.1% of subjects in the Engerix-B group. The most commonly reported medical history terms by preferred term (PT) were hypertension (35.4% Heplisav-B, 34.6% Engerix-B), seasonal allergy (22.5% Heplisav-B, 23.1% Engerix-B), depression (17.0% Heplisav-B, 17.0% Engerix-B), osteoarthritis (16.5% Heplisav-B, 16.1% Engerix-B), gastroesophageal reflux disease (15.6% Heplisav-B, 15.6% Engerix-B), and hyperlipidemia (15.2% Heplisav-B, 14.7% Engerix-B).

Reviewer comment: *In terms of distribution of medical history, the randomization appears adequate. In general, the clinical reviewer did not identify any differences between the Heplisav-B and Engerix-B arms likely to be clinically significant. Baseline rates of specific conditions of interest are discussed below and with the description of the appropriate MAEs (see Section 6.3.12.2).*

Baseline cardiac medical conditions were examined closely in the Applicant's Summary of Clinical Safety, given the safety findings of DV2-HBV-23 (Section 6.3.12.2). The tables below (Tables 13 and 14) summarize the risk factors for cardiovascular disease and pre-existing coronary artery ischemic disease between the two study groups. The reviewer generated analysis of hypertension includes slightly different PTs than that used by the Applicant, but doesn't impact the overall conclusions regarding the baseline rates of this disease.

Table 13. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population, DV2-HBV-23

Condition or characteristic	Heplisav-B N=5587 n (%)	Engerix-B N=2781 n (%)
Type 2 Diabetes*	762 (13.6)	381 (13.7)
Hypertension†	2021 (36.2)	978 (35.2)
Hyperlipidemia‡	1757 (31.4)	879 (31.6)
Sex and Age: Male > 45 years	1879 (33.6)	919 (33.0)

Condition or characteristic	Heplisav-B N=5587 n (%)	Engerix-B N=2781 n (%)
Sex and Age: Female > 55 years	1028 (18.4)	537 (19.3)
Smoking within 1 year	1843 (33.0)	909 (32.7)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)

Source: Adapted from 125428/0.42; Module 2.7.4, Summary of Clinical Safety; Table 2.7.4-27, p. 84-86
* Defined as subjects flagged by the Applicant as diabetic – subjects with a clinical diagnosis of diabetes and taking a hypoglycemic agent
† Reviewer-generated analysis using dataset ADMH, Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
‡ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term for Dyslipidemia standard MedDRA query narrow

Table 14. Number and proportion of subjects with medical conditions reported at baseline indicating cardiac ischemia, Safety Population, DV2-HBV-23

Preferred term	Heplisav-B N=5587 n (%)	Engerix-B N=2781 n (%)
At least one baseline medical diagnosis of cardiac ischemia*	**211 (3.8)**	**99 (3.6)**
Coronary artery disease	140 (2.5)	65 (2.3)
Myocardial infarction	72 (1.3)	35 (1.3)
Coronary arterial stent insertion	56 (1.0)	27 (1.0)
Coronary artery bypass	47 (0.8)	16 (0.6)
Arteriosclerosis Coronary Artery	19 (0.3)	4 (0.1)
Angina Pectoris	18 (0.3)	12 (0.4)
Ischemic Cardiomyopathy	3 (0.05)	1 (< 0.05)
Myocardial ischemia	3 (0.05)	0
Coronary Artery Occlusion	2 (0.04)	2 (0.1)
Coronary artery stenosis	2 (0.04)	0
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	1 (0.02)	1 (0.04)
Angina unstable	1 (0.02)	1 (0.04)
Arteriospasm coronary	1 (0.02)	0
Prinzmetal angina	1 (0.02)	0
Silent myocardial infarction	1 (0.02)	0
Troponin increased	1 (0.02)	0
Coronary Angioplasty	0	5 (0.2)

Source: Adapted from 125428/0.42; Module 2.7.4, Summary of Clinical Safety; Table 2.7.4-27, p. 84-86
* Defined as subjects with at least one medical history preferred term within the standard MedDRA queries narrow of Myocardial Infarction and Other Ischemic Heart Disease

There are small differences between study populations in baseline characteristics indicative of increased risk for coronary artery disease. The greatest differences are in obesity (48.8% Heplisav-B, 46.2% Engerix-B), hypertension (36.2% Heplisav-B, 35.2% Engerix-B), and female ≥ 56 years of age (18.4% Heplisav-B, 19.3% Engerix-B). There are very small differences between study populations in history of specific cardiac ischemic PTs at baseline, but the number of subjects with at least one of these conditions is balanced at baseline (3.8% Heplisav-B, 3.6% Engerix-B).

Reviewer comment: *Rates of cardiac risk factors and history of cardiac ischemic disease are similar between groups.*

The Applicant presents an analysis of subjects in the diabetes group. As per their analysis, HbA1c at baseline, the proportion of subjects with one or more complications of diabetes (84.1% Heplisav-B, 82.2% Engerix-B), and the proportion of subjects who had diabetes for 5 or more years (66.7% Heplisav-B, 67.0% Engerix-B) were similar between the treatment groups. Of the diabetic subjects tested at Week 24, 19.2% of Heplisav-B subjects and 23.3% of Engerix-B subjects had HbA1c levels < 6.5%, 62.0% of Heplisav-B subjects and 55.7% of Engerix-B subjects had HbA1c levels 6.5% to 9.0%, and 18.9% of Heplisav-B subjects and 21.1% of Engerix-B subjects had HbA1c levels > 9.0%.

Reviewer comment: *At baseline, diabetic control was the same in both treatment groups. In contrast to baseline measurements, at Week 24, there are slightly more subjects in the Heplisav-B group with diabetes that is not well-controlled (HbA1c ≥ 6.5%) (80.9%) compared to the Engerix-B group (76.7%), though the majority of these subjects have moderate, not severe, elevations in HbA1c. This is consistent with an increase in hyperglycemic MAEs reported in the Heplisav-B group.*

Prior to vaccination, the rates of subjects reporting concomitant medication use in the 28 days prior to vaccination was the same between treatment groups (77.0% Heplisav-B, 76.9% Engerix-B). Specifically, the rates of the following medication classes, which are indicative of cardiovascular disease, were similar between groups: agents acting on the renin-angiotensin system (25.2% Heplisav-B, 24.2% Engerix-B); lipid modifying agents (23.6% Heplisav-B, 23.4% Engerix-B), antithrombotic agents (15.8% Heplisav-B, 15.7% Engerix-B), drugs used in diabetes (14.2% Heplisav-B, 13.9% Engerix-B), beta blocking agents (10.4% Heplisav-B, 10.0% Engerix-B), diuretics (9.7% Heplisav-B, 8.7% Engerix-B), calcium channel blockers (8.2% Heplisav-B, 7.6% Engerix-B), anti-hypertensives (1.7% Heplisav-B, 1.2% Engerix-B), and cardiac therapy (1.3% Heplisav-B, 1.3% Engerix-B). Other classes of medications which are pertinent to MAE findings were also similar between groups: psychoanaleptics (18.2% Heplisav-B, 19.6% Engerix-B) and psycholeptics (11.2% Heplisav-B, 11.2% Engerix-B).

Reviewer comment: *The clinical reviewer identified no clinically significant differences between study groups in class of medication reported at baseline. While there are very small differences, up to 1%, which could indicate more medication use in the Heplisav-B group, it is unclear how that would influence reporting of MAEs and SAEs. More medication use could indicate that subjects in one group have more medical conditions or greater severity of medical conditions at baseline, or it could indicate that subjects in that group are being treated more aggressively and have better disease control.*

6.3.10.1.3 Subject Disposition

Subject disposition data for study DV2-HBV-23 showed that the majority of study subjects randomized to the study, completed study treatment. The overall proportion (≤ 6.5%) of subjects who discontinued the study was consistent with the proportions seen in previous phase 3 studies of Heplisav-B (studies DV2-HBV-10 and -16). The most common reason for study discontinuation was loss to follow-up (≤ 5.7% all groups), followed by withdrawal of study informed consent (≤ 1.8% all groups). The PP population, used for immunogenicity analysis, comprised approximately 82% of the

randomized study population. A summary of subject disposition is provided in Table 15 below.

Table 15. Subject Disposition, Study DV2-HBV-23

Disposition	Heplisav-B n (%)	Engerix-B n (%)	Total n (%)
Randomized	5592 (100%)	2782 (100%)	8374 (100%)
Treated	5587 (>99.9%)	2781 (>99.9%)	8368 (>99.9%)
Not treated	5 (<0.1%)	1 (<0.1%)	6 (<0.1%)
Completed Study Treatment[a]	5221 (93.4%)	2606 (93.7%)	7827 (93.5%)
Discontinued Study Treatment	366 (6.5%)	175 (6.3%)	541 (6.5%)
Completed Study[b]	5092 (91.1%)	2567 (92.3%)	7659 (91.5%)
Discontinued Study	500 (8.9%)	215 (7.7%)	715 (8.5%)
Consent withdrawn	100 (1.8%)	39 (1.4%)	139 (1.7%)
Physician Decision	8 (0.1%)	1 (<0.1%)	9 (0.1%)
Pregnancy	2 (1.0%)	2 (0.3%)	20 (0.8%)[b]
Protocol violation	1 (<0.1%)	0	1 (<0.1%)
Subject lost to follow-up	319 (5.7%)	153 (5.5%)	472 (5.6%)
Medically-attended AE	4 (<0.1%)[c]	0	4 (<0.1%)
Non-compliance	7 (0.1%)	1 (<0.1%)	8 (<0.1%)
Other	34 (0.6%)	14 (0.5%)	48 (0.6%)
Death	25 (0.4%)	(0.3%)[e]	32 (0.4%)
Per-protocol analysis population	4537 (81.1%)	2289 (82.3%)	6826 (81.5%)
Modified Intent-to-treat analysis population	5278 (94.4%)	2635 (94.7%)	7913 (94.5%)
Safety analysis population	5587 (>99.9%)	2781 (99.9%)	8368 (>99.9%)
Laboratory Safety Sub-study	207 (3.7%)	102 (3.7%)	309 (3.7%)

Source: BLA STN 125248/0.42, DV2-HBV-23, CSR, Table 10-3, page 56.
n = number of subjects
AE: adverse event
[a] Subjects who received three injections completed study treatment.
[b] Subjects who had a Week 56 visit completed the study.
[c] The four adverse events listed as the reason for study discontinuation were metastatic renal cell carcinoma, migraine, bipolar I disorder, and urticaria.

Reviewer comment: *The proportion of subjects who completed a Week 56 visit in both treatment groups is consistent with the Applicant's sample size calculation assumption that 10% of subjects would discontinue prior to study completion. The proportion of subjects that comprised the PP population was similar to that seen in the other two phase 3 studies of Heplisav-B, reviewed in the original BLA application (approximately 75-88% of the total randomized population), and was similar between treatment groups. The reasons for subject discontinuation from the study were also similar to those of studies DV2-HBV-10 and -16, with the most common reason in for discontinuation in all three studies being 'lost-to-follow-up'.*

The Applicant stated that they utilized a vendor, (b) (4) , to research the status of 271 of 469 subjects considered lost-to-follow-up, but did not describe how these 271 subjects were chosen in 125428/0.42. In the 9 September 2016 IR and an IR sent 24 April 2017, the CBER asked the Applicant to describe the process by which subjects were referred to the vendor. In their responses, 125428/0.63 and 125428/0.88, the Applicant stated that sites were solely responsible for referring subjects to the vendor and that this was optional. In order to be referred, subjects were required to be lost to follow-up, defined

as three or more unsuccessful phone attempts, and either no response to, or the return of a certified letter. Some subjects were not referred because they were still in the process of being confirmed as lost-to-follow-up at the time of study completion. However, the Applicant also stated that "the site may have considered the lack of response a lack of interest, and the subject would not have been referred to the search vendor." In 125428/0.88, the Applicant states that 172 Heplisav-B subjects and 73 Engerix-B subjects were lost-to-follow-up and not referred to the vendor.

Reviewer comment: *There does not appear to have been a systematic way to refer lost-to-follow-up subjects to the vendor. Slightly more Heplisav-B recipients were not referred to the vendor for the re-engagement process (2.4:1 compared to a 2:1 randomization), which could potentially introduce bias. However, overall, the rate of subjects lost-to-follow-up is low.*

Additional analysis of the PP population examined reasons for study exclusion, which are provided in Table 16 below:

Table 16. Reasons for Exclusion, Per Protocol Population, Study DV2-HBV-23

Study Population and Exclusion Reason	Heplisav-B N=5592 n (%)	Engerix- B N=2782 n (%)	Total N=8374 n (%)
PP Population	4537 (81.1%)	2289 (82.3%)	6826 (81.5%)
Total Excluded Subjects	1055 (18.9%)	493 (17.7%)	1548 (18.5%)
Not meeting ≥ one enrollment criteria	67 (1.2%)	36 (1.3%)	103 (1.2%)
Pre-existing autoimmune disorder	39 (0.7%)	23 (0.8%)	62 (0.7%)
Receipt of exclusionary medication/blood product	19 (0.3%)	8 (0.3%)	27 (0.3%)
Other	9 (0.2%)	5 (0.2%)	14 (0.2%)
Mis-stratified by diabetic status/age	26 (0.5%)	10 (0.4%)	36 (0.4%)
Did not receive correct vaccine as randomized	0	0	0
Did not receive all study injections	371 (6.6%)	176 (6.3%)	547 (6.5%)
Vaccine given outside window	164 (2.9%)	76 (2.7%)	240 (2.9%)
Anti-HBs serum sample collected outside four weeks (± 7 days)	190 (3.4%)	86 (3.1%)	276 (3.3%)
No anti-HBs levels obtained at Week 28	431 (7.7%)	188 (6.8%)	619 (7.4%)
Received prohibited concomitant medications	217 (3.9%)	113 (4.1%)	330 (3.9%)
Systemic corticosteroids	209 (3.7%)	112 (4.0%)	321 (3.8%)
Other immunomodulators or immune suppressive medications (exception inhaled steroids)	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1)
Blood products or immunoglobulin	9 (0.2%)	0	9 (0.1)
DNA plasmids or oligonucleotides	0	0	0
Other investigational medication	0	1 (< 0.1%)	1 (< 0.1%)
Other	0	0	0

Source: BLA STN 125248/0.42, DV2-HBV-23, CSR, Table 10-2, page 53, Tables 14.1.1.2 and 14.1.1.4.
N = number of subjects per treatment group
n = number of subjects with each characteristic
Anti-HBs: antibody against hepatitis B surface antigen; DNA: deoxyribonucleic acid
PP: Per protocol

Reviewer comment: *The reasons provided for exclusion from the PP population are consistent with those seen in studies DV2-HBV-10 and -16 and deemed reasonable by*

the clinical reviewer. The percentage of subjects excluded from the PP population was similar between treatment groups for study DV2-HBV-23 (18-19%) and within the range of the percentage of subjects excluded from the PP population in studies DV2-HBV-10 and -16 (14-24%).

For study DV2-HBV-23 the most common reason for exclusion (in decreasing order) was: lack of immunogenicity testing at Week 28, subjects not receiving all study vaccinations, receipt of prohibited concomitant medications, collection of the anti-HBs serum sample outside the specified window, and receipt of vaccination outside the visit window at Week 4.

Of subjects excluded from the PP population, 19.6% of Heplisav-B subjects and 18.0% of Engerix-B subjects had a major protocol deviation. The most frequent major protocol deviations were visits outside of the visit schedule (for example Week 4 visit occurred out of window), procedures and tests that were not performed according to protocol (for example: anti-HBs serum sample collected outside the pre-specified window), and subjects taking a disallowed medication (for example systemic corticosteroids given for ≥ three consecutive days). A summary of major protocol deviations for the randomized population is provided in Table 17 below.

Table 17. Major Protocol Deviations, Randomized Population, Study DV2-HBV-23

Deviation Category	Heplisav-B n (%)[a]	Engerix- B n (%)[a]	Total n (%)[a]
Number of randomized subjects	5592 (100%)	2782 (100%)	8374 (100%)
Total protocol deviations	3734	1799	5533
Major protocol deviations	1729 (46.3%)	803 (44.6%)	2532 (45.8%)
Visit Schedule	644 (17.2%)	293 (16.3%)	937 (16.9%)
Procedures/Tests	484 (13.0%)	230 (12.8%)	714 (12.9%)
Disallowed Medications	330 (8.8%)	171 (9.5%)	501 (9.1%)
Investigational Product Administered	82 (2.2%)	34 (1.9%)	116 (2.1%)
Informed Consent	67 (1.8%)	18 (1.0%)	85 (1.5%)
Inclusion/Exclusion Criteria	57 (1.5%)	24 (1.3%)	81 (1.5%)
Other	33 (0.9%)	16 (0.9%)	49 (0.9%)
MAE/SAE	31 (0.8%)	18 (0.9%)	48 (0.9%)
Withdrawal Criteria	1 (< 0.1%)	0	1 (<0.1%)

Source: BLA STN 125248/042, DV2-HBV-23, CSR, Table 10-4, page 57, Table 14.1.5.1.
n = number of subjects
MAE medically-attended adverse event; SAE: serious adverse event.
[a]Denominators for percentage are the total number of protocol deviations for each column.

Reviewer comment: *Since subjects with comorbidities were allowed to enroll in this study, the types of major protocol deviations seen were not unexpected, but more likely reflected the study population enrolled in DV2-HBV-23.*

In response to the 9 September 2016, in 125428/0.63, the Applicant clarified that subjects with a major protocol deviation of MAE/SAE were subjects with an AESI, SAE, or pregnancy that was reported to the site outside of the 24-hour window. Subjects with this major protocol deviation were not excluded from the analysis populations due to this deviation.

Site Level Unblinding
The CSR for study DV2-HBV-23 stated that the treatment assignments of several subjects were prematurely known to study personnel who should not have had access to this information, thereby resulting in accidental unblinding of these subjects. There were seven sites involving nine subjects where the study subjects were accidentally unblinded. In addition, the principal investigator at Site 124 was unblinded to treatment assignment on two separate occasions by signing follow-up letters from the unblinded site monitor that contained treatment assignment information on several subjects. This investigator was instructed to restrict further contact with the subjects that were unblinded and the subinvestigator assumed responsibility for safety assessment and follow-up care.

Reviewer comment: *The clinical reviewer's assessment of the information the Applicant provided in the CSR regarding the handling of accidental unblinding is that it appears reasonable. The handling appears to have been addressed in a way to reduce potential bias.*

Subject Unblinding at the Level of the Applicant/CRO
Also, described in the CSR were nine occasions involving 145 subjects where study team personnel at Dynavax and/or the CRO, (b) (4), prematurely received information regarding treatment assignment of several subjects and became accidentally unblinded. These various instances included: access of study personnel to unblinded vial assignment reports, access to the unblinded subject dosing worksheets, and receipt of communications (for example, email) which included unblinded subject information. Based on the total number of randomized subjects, the impact of this excursion was negligible (< 2% of randomized subjects).

Reviewer comment: *The overall impact of this excursion involving 145 subjects, given the large number of subjects enrolled, was minimal. Nonetheless, the finding of unblinding in this study suggested potential Quality Control issues. The BIMO reviewer recommended requests for further information to support an assessment be included in the CR letter (10 November 2016 CR comments 41 and 42).*

BIMO Inspection Findings of Study DV2-HBV-23, Site 122/222:
BIMO's inspections found that for sites 122/222 (n=719, 8.6% total subject enrollees), of the total 76 subjects chosen for audit at this site, 15 subjects were classified as being 'lost to follow-up' (LTFU) (see email correspondence Bhanu Kannan, 2 November 2016 and 3 November 2016). Of these 15 LTFU subjects, 12 randomly selected LTFU subjects were identified and three of these subjects (25%, 3/12) were further identified as having been incorrectly classified as 'per protocol' population subjects. The three subjects were found to have a major protocol deviation (based on the having an out-of-window Week 28 visit and blood sampling) which should have precluded inclusion into the per protocol population.

Also, provided with the preliminary BIMO inspection results, was the BIMO inspector's finding that the protocol deviation log for study DV2-HBV-23 was maintained as an Excel spreadsheet without any access control or password protection. This finding raised the theoretical concern protocol deviation data could be easily manipulated or changed.

In the 8 February 2017 CR response and 6 April 2017 IR response, the Applicant provided an explanation for the handling of protocol deviation subjects and handling of

subjects who were lost to follow-up and subsequently re-engaged. In addition, the Applicant verified that the information in the protocol deviation log was complete and accurate.

Reviewer comment: *Responses to CR items 41 and 42 were reviewed by BIMO and found to be acceptable and adequately addressed.*

6.3.11 Efficacy Analyses

The efficacy analysis of study DV2-HBV-23 was an immunogenicity-based effectiveness evaluation focused on the comparison of the SPR between Heplisav-B and Engerix-B in the general adult population. Subgroup analyses by diabetic status, BMI, or smoking status were evaluated, to demonstrate that Heplisav-B was immunogenic in these populations, when compared to the general adult population.

6.3.11.1 Analyses of Primary Endpoint(s)

The Applicant's primary immunogenicity endpoint was defined as the comparison of the SPR induced by Heplisav-B to that induced by Engerix-B at Week 28, in subjects with type 2 diabetes. Additional sensitivity analyses were performed to account for factors such as diabetes severity, duration and diabetes control (as determined by blood HbA1c level).

Study subjects were determined to have type 2 diabetes based on clinical diagnosis and a requirement that they be taking either an oral or non-insulin injectable hypoglycemic agent and/or insulin for control of blood glucose levels.

HbA1c at baseline, the proportion of subjects with one or more complications of diabetes (84.1% Heplisav-B, 82.2% Engerix-B), and the proportion of subjects who had diabetes for 5 or more years (66.7% Heplisav-B, 67.0% Engerix-B) were similar between the two treatment groups. For both treatment arms, approximately one fourth of diabetic subjects had an HbA1c < 6.5% at baseline—consistent with good glucose control, with slightly more than half having an HbA1c ranging between 6.5-9.0% at baseline, and the rest > 9.0%. These data indicate that the majority of diabetic subjects enrolled in study DV2-HBV-23 did not have baseline blood glucose levels controlled at target levels.[26]

Of the diabetic subjects tested at Week 24, 19.2% of Heplisav-B subjects and 23.3% of Engerix-B subjects had HbA1C levels < 6.5%, 62.0% of Heplisav-B subjects and 55.7% of Engerix-B subjects had HbA1C levels 6.5% to 9.0%, and 18.9% of Heplisav-B subjects and 21.1% of Engerix-B subjects had HbA1C levels > 9.0%. The majority of type 2 diabetic subjects in both treatment arms were obese (mean BMI in Heplisav-B group: 35.2 kg, mean BMI in Engerix-B group: 35.2 kg).

Reviewer comment: *Verification by the statistical reviewer of the diabetic subgroup population for potential imbalance between the two treatment arms by demographic factors and medical conditions was performed based on: age group, sex, BMI stratum, race and smoking, using a chi-square test. The Heplisav-B and Engerix-B diabetic populations were comparable across these variables, and also comparable with regard to diabetes severity and control.*

The comparison of the SPR at Week 28 in type 2 diabetics vaccinated with Heplisav-B and Engerix-B is presented in Table 18 below.

Table 18. Primary Immunogenicity Endpoint Analysis: Comparison of Seroprotection Rates between Heplisav-B and Engerix-B at Week 28 in Subjects with Type 2 Diabetes, Per Protocol Analysis Population, DV2-HBV-23

Visit	Heplisav-B[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Heplisav-B- Engerix-B) (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
Week 28	90.0 % (87.4, 92.2)[c] 576/640	65.1 % (59.6, 70.3)[d] (209/321)	24.9 (19.3, -30.7)	Yes

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-1, page 67.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% Cis were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method was used to calculate the 95% confidence interval.

The primary immunogenicity analysis showed that the SPR in the Heplisav-B group at Week 28 was numerically higher than in the Engerix-B group at Week 28. The difference between the SPRs (Heplisav-B minus Engerix-B) was 24.9% (95% CI: 19.3, -30.7), which met the prospectively defined criterion of non-inferiority (lower limit of the 95% CI > 0%).

Sensitivity analysis for the primary immunogenicity endpoints examined the effect of the duration of diabetes (< 5 years vs. ≥ 5 years), baseline HbA1c level (< 6.5%, 6.5%-9.0%, and > 9.0%), the number of diabetes complications, metformin use (an oral hypoglycemic), immunosuppressive medication use, as well as treatment group, age, sex, race, BMI, and smoking history. Stepwise logistic regression found that treatment group (Heplisav-B vs. Engerix-B), age and BMI affected the level of SPR at significance level below 0.05. None of the diabetes variables affected the SPR. Older and obese subjects were less likely to be seroprotected than younger and non-obese subjects.

Reviewer comment: *Independent of treatment arm, age and obesity were factors that affected SPRs post-vaccination. Because the Heplisav-B and Engerix-B arms were relatively balanced in terms of age and BMI, the SPRs seen in type 2 diabetics in the primary immunogenicity analysis were less likely to be affected by these independent factors.*

6.3.11.2 Analyses of Secondary Endpoints

CBER reviewed the secondary immunogenicity endpoint of the non-inferiority of the SPR at Week 24 in Heplisav-B recipients compared with the SPR at Week 28 in Engerix-B recipients in all per protocol subjects in study DV2-HBV23, to confirm that results observed in this study were consistent with per protocol population findings in studies DV2-HBV-10 and -16. SPRs were 95.4 % (95% CI 94.8, 96) for Heplisav-B recipients and 81.3% (79.6, 82.8) for Engerix-B recipients with an estimated difference in SPR of -14.2 (-12.5, -15.9) (See Table 19 below). Non-inferiority criteria were met, as the upper bound of the 95% CI of the estimated difference in SPR was < 10%, and these results were consistent with those observed in studies DV2-HBV-10 and -16.

Table 19. Secondary Immunogenicity Endpoint Analysis: Comparison of Peak Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28), Per Protocol Analysis Population, Study DV2-HBV-23

Visit	Heplisav-B[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Heplisav-B – Engerix-B) (95%) CI)	Non-inferiority Criteria Met?[e] (Yes/No)
Week 24/ Week 28	95.4 % (94.8, 96.0)[c] 4176/4376	81.3 % (79.6, 82.8)[d] (1860/2289)	14.2 (12.5, -15.9)	Yes

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-2, page 68.
CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method was used to calculate the 95% confidence interval.
[e] Noninferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).

Reviewer comment: *Although study DV2-HBV-23's primary purpose was to address VRBPAC's concerns in 2012 regarding the size of the safety database for Heplisav-B, this immunogenicity endpoint is included in this review, in order to show that the SPR results for the per protocol population in study DV2-HBV-23 was comparable to that seen in studies DV2-HBV-10 and -16. Non-inferiority was demonstrated between Heplisav-B and the active comparator, Engerix-B.*

6.3.11.3 Subpopulation Analyses

Results of subpopulation analyses are included in this review by demographic subgroups (age, sex and race) to show the immune response to Heplisav-B in these populations. In addition, subgroup analysis of immunogenicity by BMI and smoking status is included.[27, 28]

A comparison of the SPR at Week 24 in Heplisav-B subjects to the SPR at Week 28 in Engerix-B subjects is presented in Table 20 below. As prespecified in the CSR, enrollment in DV2-HBV-23 was stratified by age, using the 18-39 and 40-70-year age groups. However, presentation of SPR data by age subgroup, used a different set of age ranges than those pre-specified for randomization, as specified in the statistical analysis plan. For the age subgroup comparison between Heplisav-B and Engerix-B, SPR data were presented for the following age ranges: the 18-29 year, 30-39 year, 40-49 year, 50-59 year, and 60+ year age groups.

Table 20. Comparison of Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28) by Age, Overall Per Protocol Analysis Population, DV2-HBV-23

Age Group (Years)	n/N	Heplisav-B[a] SPR (%) (95% CI)[c]	n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Estimated Difference in SPR[c] (Heplisav-B − Engerix-B) (95% CI)[d]
18-29	174/174	100.0 (97.9, 100.0)	93/99	93.9 (87.3, 97.7)	6.1 (2.8, 12.6)
30-39	625/632	98.9 (97.7, 99.6)	300/326	92.0 (88.5, 94.7)	6.9 (4.2, 10.4)
40-49	947/974	97.2 (96.0, 98.2)	436/518	84.2 (80.7, 87.2)	13.1 (9.9, 16.6)
50-59	1370/1439	95.2 (94.0, 96.3)	604/758	79.7 (76.6, 82.5)	15.5 (12.6, 18.7)
60+	1060/1157	91.6 (89.9, 93.1)	427/588	72.6 (68.8, 76.2)	19.0 (15.2, 23.0)

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-3, page 69.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method was used to calculate the 95% confidence interval.

SPR rates for both treatment arms were highest in younger subjects (18-29 years of age), steadily decreasing with each subsequent age group, and lowest in the age 60+ age group. Despite the expected decrease in SPR with increasing age the SPR rates at Week 28 for Heplisav-B vaccinated subjects in study DV2-HBV-23 were high in all age groups (> 91%).

SPR comparison based on sex, showed similar SPRs in male and female subjects immunized with Heplisav-B (> 94%), also showing a robust immune response for both sexes (see Table 21 below).

Table 21. Comparison of Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28) by Sex, Overall Per Protocol Analysis Population, DV2-HBV-23

Sex	n/N	Heplisav-B[a] SPR (%) (95% CI)[c]	n/N	Engerix-B[b] SPR (%) (95%CI)[c]	Estimated Difference in SPR (Heplisav-B − Engerix-B) (95% CI)[d]
Male	2082/2203	94.5 (93.5, 95.4)	906/1150	78.8 (76.3, 81.1)	15.7 (13.2, 18.3)

Sex	n/N	Heplisav-B[a] SPR (%) (95% CI)[c]	n/N	Engerix-B[b] SPR (%) (95%CI)[c]	Estimated Difference in SPR (Heplisav-B − Engerix-B) (95% CI)[d]
Female	2094/2173	96.4 (95.5, 97.1)	954/1139	83.8 (81.5, 85.9)	12.6 (10.4, 15.0)

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-4, page 69.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method was used to calculate the 95% confidence interval.

The last demographic subgroup analysis comprised a comparison of SPRs by race. During the 2012 VRBPAC advisory committee meeting, the need for greater inclusion and representation of all racial groups was voiced. A review of racial representation in DV2-HBV-23 showed a continued lack of enrichment of this study with more Asian subjects, albeit an increased proportion of Black or African American subjects compared to DV2-HBV-10 and -16. The majority of subjects enrolled were white, followed by African Americans. Asians represented approximately 1% of the total study population in DV2-HBV-23.

Based on the SPR data in DV2-HBV-23, all racial subgroups evaluated who received Heplisav-B had similar immune responses at Week 28, all of which were > 94% (Table 22).

Table 22. Comparison of Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28) by Race, Overall Per Protocol Analysis Population, DV2-HBV-23

Race[e]	n/N	Heplisav-B[a] SPR (%) (95%CI)[c]	n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Estimated Difference in SPR[d] (Heplisav-B − Engerix-B) (95% CI)[d]
White	2910/3084	94.4 (93.5, 95.1)	1350/1675	80.6 (78.6, 82.5)	13.8 (11.7, 15.9)
Black or African American	1147/1169	98.1 (97.2, 98.8)	456/554	82.3 (78.9, 85.4)	15.8 (12.7, 19.3)
Asian	43/45	95.6 (84.9, 99.5)	27/29	93.1 (77.2, 99.2)	2.5 (-9.3, 18.2)
Other	74/76	97.4 (90.8, 99.7)	27/31	87.1 (70.2, 96.4)	10.3 (0.6, 26.6)

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-7, page 71.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method without stratification was used to calculate the 95% confidence interval.

[e] Race was unknown for two Heplisav-B subjects.

Additional subgroup analyses of immunogenicity were performed based on body mass index (BMI) and smoking status. The Applicant indicated that these analyses were performed to assess whether the immune response to Heplisav-B in these subgroups, generally considered representative of subjects with an impaired immune response to hepatitis B vaccines,[27] might be similar to those seen in healthy individuals.

Evaluation of SPR by body mass index (BMI) was performed by comparing subjects who were defined as being obese or non-obese. Obesity was defined as a BMI ≥ 30 kg/m^2 at baseline, an accepted definition of obesity.[29]

The Applicant pre-specified a comparison of non-inferiority of SPR in obese subjects who received Heplisav-B compared with obese subjects who received Engerix-B. Similarly, a non-inferiority comparison of SPRs was conducted for non-obese subjects who received Heplisav-B, compared with non-obese subjects who received Engerix-B. Obese and non-obese subjects had comparable SPRs at Week 28 in the Heplisav-B arm (94.7% vs. 96.1%), indicating that Heplisav-B induced a strong immune response in obese subjects (Table 23).

Table 23. Comparison of Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28) by BMI Category, Per Protocol Analysis Population, DV2-HBV-23

BMI Category[e]	n/N	Heplisav-B[a] SPR (%) (95% CI)[c]	n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Estimated Difference in SPR[c] (Heplisav-B − Engerix-B) (95% CI)[d]
Obese[f]	2051/2165	94.7 (93.7, 95.6)	811/1076	75.4 (72.7, 77.9)	19.4 (16.7, 22.2)
Non-obese	2122/2208	96.1 (95.2, 96.9)	1049/1212	86.6 (84.5, 88.4)	9.6 (7.6, 11.7)

Source: BLA 125248/0.42, DV2-HBV-23, CSR, Table 11-5, page 70.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method was used to calculate the 95% confidence interval.
[e] Three Heplisav-B and one Engerix-B subject did not have body weight available, therefore their body mass indices (BMI's) are unknown.
[f] Obesity is defined as BMI ≥ 30 kg/m^2 at baseline.

Because smoking has been identified as another factor associated with a suppressed immune response to hepatitis B vaccination,[27] evaluation of SPRs by smoking status was performed to ascertain whether Heplisav-B might afford adequate protection against hepatitis B infection in this subgroup.

Smokers were defined as those subjects having a smoking history in the past year (yes/no answer). Stratification of smokers by pack per day smoking history or years smoked was not performed in this study, thereby limiting conclusions that could be made regarding comparability of subjects defined as being 'smokers' or assessing the severity

of their smoking history and potential impact on immunosuppression and overall health status.

Reviewer comment*: Descriptive qualities were not provided in the Applicant's definition of a 'smoker' (e.g., stratification of smokers by pack per day smoking history or years smoked), thereby potentially limiting conclusions regarding comparability of subjects regarding tobacco exposure and any potential impact on immunosuppression and overall health status. Because of the smoking definition used, smokers who stopped smoking one year prior to study enrollment would not have been classified as smokers, regardless of prior years of use. Furthermore, this definition of smoker is likely not the most appropriate definition to capture individuals who are at increased risk of cardiovascular and other diseases due to smoking.*

A comparison of SPRs between smokers and non-smokers showed little difference between both, in the Heplisav-B arm, with both subgroups having SPRs > 95% at Week 28 in study DV2-HBV-23 (Table 24). A robust immune response to Heplisav-B was demonstrated in both subgroups, a finding which raises the issue of whether the criteria for categorizing a subject as a 'smoker' or 'non-smoker' was clinically predictive of immune response, since within each treatment group, this categorization did not affect the difference in the SPR to any great degree.

Table 24. Comparison of Seroprotection Rates between Heplisav-B (Week 24) and Engerix-B (Week 28) by Smoking Status, Per Protocol Analysis Population, DV2-HBV-23

Smoking Status	n/N	Heplisav-B[a] SPR (%) (95% CI)[c]	n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Estimated Difference in SPR[c] (Heplisav-B − Engerix-B) (95% CI)[d]
Smokers	1315/1371	95.9 (94.7, 96.9)	559/711	78.6 (75.4, 81.6)	17.3 (14.2, 20.6)
Non-smokers	2861/3005	95.2 (94.4, 95.9)	1301/1578	82.4 (80.5, 84.3)	12.8 (10.8, 14.8)

Source: BLA 125248/042, DV2-HBV-23, CSR, Table 11-6, page 71.
CI = Confidence interval, N = number of evaluable subjects, n = number of seroprotected subjects; SPR: Seroprotection rate.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).
[b] Study injections were given at Weeks 0, 4, 24.
[c] 95% CIs were calculated using the two-sided Clopper-Pearson method.
[d] The Miettinen and Nurminen method without stratification was used to calculate the 95% confidence interval.

Reviewer comment and conclusion*: An evaluation of SPR in Heplisav-B-vaccinated subjects by demographic subgroups (age, sex, and race) and by medical conditions (obesity) showed that Heplisav-B was immunogenic in these subgroups (SPR > 90%).*

Conclusions regarding the immune response to Heplisav-B in smokers is limited by the definition of smoking status which did not include the amount or duration of smoking. The reviewer is unable to determine how representative the group of smokers studied in study DV2-HBV-23 is, of the population of smokers in the U.S. and whether this subgroup appropriately represents an immunosuppressed population less likely to respond to immunization against hepatitis B.

6.3.11.4 Dropouts and/or Discontinuations

Data from subjects who dropped out of the study were not imputed. A discussion of subject discontinuations is provided in Section 6.3.10.1.3.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

MAEs, SAEs, and AESIs were monitored from screening through Week 56. Solicited AEs and unsolicited, non-medically-attended events were not reported, as agreed to by CBER based on the results of data obtained in previous studies. Adverse events were assessed through clinic visits (Weeks 0, 4, 24, 28, and 56) and through internet questionnaires about health care encounters at Weeks 8, 40, and 52.

The severity of MAEs and laboratory abnormalities were graded based on "Guidance for Industry: Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." All fatal MAEs were to be graded as Grade 5. All MAEs not listed in the CBER toxicity grading scale were graded as follows:

Grade 1 – Mild
No interference with activity
Grade 2 – Moderate
Some interference with activity, not requiring medical attention
Grade 3 – Severe
Prevents daily activity and requires medical attention
Grade 4 – Potentially life-threatening
Emergency room visit or hospitalization
Grade 5 – Death

The protocol specified that for all MAEs and SAEs, if there was a change in the severity after onset, the event was to be reported as a single entry with the maximum severity grading captured.

Through the course of the review, several AEs were identified that appeared to be the same event but were reported more than once with a change in the seriousness of the event (MAE to SAE). These events had the same or similar PT and the end date of one

was the same as the start date of the next. The Applicant responded to a question regarding this issue in the 9 September 2016 IR in 125428/0.68. The Applicant identified 19 subjects with an event captured as both an MAE and an SAE.

Reviewer comment: *While this would be expected to impact event counts and subject counts when PTs for these events are different (for example chest pain then angina pectoris), the number of events identified was low and is not expected to impact overall safety assessment.*

Relationship was assessed by the investigator based on the following definitions:

Not Related	Another cause of the event is most plausible; or clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; or a causal relationship is considered biologically implausible.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
Probably Related	An event that follows a reasonable temporal sequence from administration of the study treatment, and there is a biologically plausible mechanism for study treatment causing or contributing to the AE [adverse event], and the event could not be reasonably explained by the known characteristics of the subject's clinical state. In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

Please see the procedures for assessment of AESIs in Section 6.3.7 above.

In reviewing the data submitted, in order to evaluate adverse events, the reviewer looked at individual PTs, but also grouped events by using the standardized MedDRA query (SMQ) and higher level terms (HLTs), when these groupings were available and appropriate. The SMQ is a validated, pre-determined set of MedDRA terms used to facilitate the retrieval of MedDRA coded data as a first step in investigating safety issues. HLTs are another grouping utilized in MedDRA, by which related PTs are grouped together based upon anatomy, pathology, physiology, etiology or function.[30] No criteria were pre-specified that would signal a safety event warranting further investigation. Several methods were used by the clinical reviewer to identify AEs that were reported at higher rates, judged to be potentially clinically significant, in the Heplisav-B group compared to the Engerix-B group (relative risk, lower bound of the 95% CI for relative risk, events occurring exclusively in the Engerix-B group) also considering severity, timing, and potential biologic mechanisms. For completeness, similar criteria are shown for Engerix-B when appropriate.

6.3.12.2 Overview of Adverse Events

Imbalances were noted between study groups in deaths due to all causes, cardiac SAEs (driven by an imbalance in acute myocardial infarction (AMI)), AESIs (in particular, Bell's palsy), and the medically attended event of herpes zoster.

Table 25. Summary of safety outcomes, including selected adverse events with potentially clinically significant differences between treatment groups by treatment group, Safety Population, Study DV2-HBV-23

Adverse Event	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Deaths	25 (0.45)	7 (0.25)
Serious adverse events	345 (6.2)	148 (5.3)
Cardiac serious adverse events	51 (0.91)	15 (0.54)
- Acute myocardial infarction	14 (0.25)	1 (0.04)
SEAC-assessed, new-onset autoimmune events	4 (0.07)	0
New-onset immune-mediated adverse events	9 (0.16)	1 (0.04)
- Bell's palsy	5 (0.09)	1 (0.04)
Medically Attended Events	2569 (46.0)	1286 (46.2)
- Herpes zoster‡	38 (0.7)	9 (0.3)

Source: Adapted from BLA STN 125428/0.42, DV2-HBV-23, CSR 12.2, p. 79
‡ MAEs reported in at least 0.5% of the Heplisav-B group and at at least twice the rate of the Engerix-B group.

Reviewer comment: *In the opinion of the clinical reviewer, the greater proportions of subjects who received Heplisav-B and reported deaths, cardiac SAEs, AMI, and AESIs are clinically significant given the degree of the imbalance and the potential severity of the adverse events. Please see a full discussion of these events below.*

Medically-Attended Adverse Events

The rate of MAEs (including SAEs) reported from vaccination through Week 56 study visit was approximately 46% in both study groups. In the 56-week study period, 902 subjects in the Heplisav-B group (16.1%) and 422 subjects in the Engerix-B group (15.2%) had MAEs (including SAEs) assessed as Grade 3. In the 56-week study period, 58 subjects in the Heplisav-B group (1.0%) and 45 subjects in the Engerix-B group (1.6%) had MAEs assessed as possibly or probably related by the investigator.

Reviewer comment: *The rates of MAEs, Grade 3 MAEs, and MAEs assessed as related were similar or lower in the Heplisav-B group compared to the Engerix-B group.*

The most common MAEs (>1%) in the Heplisav-B group are presented in the table below.

Table 26. Number and percent of subjects reporting common (>1%) medically attended adverse events from vaccination through Week 56 by treatment group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Upper respiratory tract infection	192 (3.44%)	92 (3.31%)
Bronchitis	176 (3.15%)	102 (3.67%)
Sinusitis	149 (2.67%)	84 (3.02%)
Hypertension	133 (2.38%)	59 (2.12%)
Urinary tract infection	132 (2.36%)	64 (2.30%)
Back pain	116 (2.08%)	54 (1.94%)
Arthralgia	98 (1.75%)	54 (1.94%)

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Osteoarthritis	77 (1.38%)	32 (1.15%)
Pain in extremity	72 (1.29%)	28 (1.01%)
Type 2 diabetes mellitus	67 (1.20%)	37 (1.33%)
Cough	62 (1.11%)	37 (1.33%)
Acute sinusitis	59 (1.06%)	37 (1.33%)

Source: Adapted from BLA STN 125428/0.42, DV2-HBV-23 CSR, Table 12-3, p. 80
N number of subjects in each treatment group
n = number of subjects reporting event

Reviewer comment: *The most commonly reported MAEs were common complaints in an adult population and were reported at similar rates between study groups.*

Engerix-B has an established safety record. Imprecision in rate estimates in this group can be amplified given the smaller sample size of Engerix-B due to the randomization ratio.

The table below shows the events that were reported in at least 0.2% in the Heplisav-B group and at at least twice the rate of the Engerix-B group. Preferred terms that are likely to represent the same or very similar events are presented together.

Table 27. Number and percent of subjects reporting medically attended events from vaccination through Week 56 in at least 0.2% in the Heplisav-B group and at at least twice the rate of the Engerix-B group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Herpes zoster	38 (0.68%)	9 (0.32%)
Atrial fibrillation	16 (0.29%)	3 (0.11%)
Drug hypersensitivity	15 (0.27%)	3 (0.11%)
Bipolar and Bipolar I Disorder	15 (0.27%)	2 (0.07%)
Acute myocardial infarction	14 (0.25%)	1 (0.04%)
Fungal infection	13 (0.23%)	2 (0.07%)
Hordeolum	11 (0.20%)	2 (0.07%)
Ingrowing nail	11 (0.20%)	2 (0.07%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, study DV2-HBV-23, dataset ADAE.
N = number of subjects in each treatment group
n = number of subjects reporting event

Herpes zoster was the only MAE PT that was reported in at least 0.5% of the Heplisav-B group and at at least twice the rate of the Engerix-B group.

Reviewer comment: *Several of the events included in the table above are likely to have occurred by chance because 1) they are common and non-serious events and/or 2) analyses combining them with other very similar events eliminated the imbalance. For example, there was no imbalance between treatment groups when all fungal infections were considered.*

Other numerical imbalances in MAEs judged potentially clinically significant by the clinical reviewer were atrial fibrillation, drug hypersensitivity, bipolar/bipolar 1 disorder, and AMI. In the 10 November 2016 CR letter, the Applicant was asked for their assessment of these MAEs, in which small, but potentially clinically significant imbalances, unfavorable to Heplisav-B were observed. A summary of their response (125428/0.74) to the imbalances in the MAEs of herpes zoster and drug hypersensitivity follows. Please see Section, 6.3.12.4 for a discussion of imbalances in SAEs, including AMI, atrial fibrillation (MAEs, but discussed with the cardiac imbalances), and bipolar disorder.

Herpes zoster: The Applicant identified one MAE PT that occurred at what they considered a statistically significantly increased rate, defined as a lower bound of the 95% exact CI > 1, in the Heplisav-B group compared to the Engerix-B group – herpes zoster. MAEs of herpes zoster were observed throughout the study duration. Through 42 days after the second dose 0.13% of Heplisav-B recipients and 0.04% of Engerix-B recipients reported herpes zoster. Through Week 28, 0.36% of Heplisav-B recipients and 0.18% of Engerix-B recipients reported Herpes zoster. The remainder of events of Herpes zoster were reported in the last six months of the study (0.32% of Heplisav-B recipients and 0.14% Engerix-B recipients). The Applicant notes a greater imbalance in events later in the follow-up period, with 11 subjects in the Heplisav-B group and 1 subject in the Engerix-B group reporting Herpes zoster after study day 320.

Reviewer comment: *The RR of Herpes zoster in the Heplisav-B group compared to the Engerix-B group is approximately 2 throughout the monitoring period. Based on the different vaccination schedules, in a comparison of events reported within 42 days after any vaccination, subjects in the Heplisav-B group have 70 days of observation, while subjects in the Engerix-B group have 112 days of observation. Therefore, one might expect 1.6 times the proportion of subjects with zoster in the Engerix-B group compared to the Heplisav-B group during this time, or 0.03% of subjects reporting herpes zoster within 42 days of vaccination in the Heplisav-B group.*

Subjects reporting herpes zoster were on average 53 years of age in the Heplisav-B group (SD 10.2, median 53, range 29 - 69) and 57 years of age in the Engerix-B group (SD 11.9, median 59, range 32 - 69). The Applicant provides population-based estimates for herpes zoster based upon Behavioral Risk Factor Surveillance System (BRFSS) (self-reports of herpes zoster) and concludes that while the incidence in the Heplisav-B group was similar to slightly higher (4.8/1000 person-years in 25 – 44 year-olds in DV2-HBV-23 compared to 4.9/1000 person years in BRFSS; 7.8/1000 person-years in 45 – 65 year-olds in DV2-HBV-23 compared to 6.8/1000 person-years in BFRSS), the incidence in the Engerix-B group was below these estimates (1.2/1000 person-years in 25 – 44 year-olds in DV2-HBV-23 compared to 4.9/1000 person years in BRFSS; 3.1/1000 person-years in 45 – 65 year-olds in DV2-HBV-23 compared to 6.8/1000 person-years in BFRSS). The incidence of herpes zoster in demographic subgroups was consistent with that published in the literature (higher in older subjects, women, and white subjects). They note that the imbalance was observed in only study DV2-HBV-23, not in other trials of Heplisav-B. In study DV2-HBV-10, with a randomization ratio of 3:1, 3 events in the Heplisav-B and 0 events in the Engerix-B group were reported. In study DV2-HBV-16, with a randomization ratio of 4:1, 4 events in the Heplisav-B and 1 event in the Engerix-B arm were reported. Finally, they posit that there is no known biologically plausible mechanism in which stimulation of TLR9

increases risk for herpes zoster, noting that murine models suggest TLR9 plays an important role in responding to varicella infection.

Reviewer comment: *Subjects reporting herpes zoster in the Heplisav-B group were younger than subjects reporting herpes zoster in the Engerix-B group. The use of the BFRSS for population-based estimates may be appropriate as investigators may not have been subjects' primary physicians and rashes may not have been clinically confirmed. Comparison to medically-confirmed incidence rates would suggest rates were higher in the Heplisav-B group, and lower in the Engerix-B group, compared to the general population. Previous studies did not identify a safety concern with regard to herpes zoster. However, the reviewer notes that the rate in the Heplisav-B group (0.2%) in studies DV2-HBV-10 and -16 is roughly twice that in the Engerix-B group (0.1%). The imbalance in study DV2-HBV-23 is noted early following vaccination and persists throughout the one-year study follow-up. One subject in DV2-HBV-23 reported zoster (115 days after dose 1 of Heplisav-B) and reported an MI (294 days after dose1) (please see the discussion of MI in 6.3.12.4). No subjects who reported zoster reported AESIs. It is possible that the imbalance in herpes zoster occurred by chance. However, the clinical reviewer cannot determine definitively that this is the case. It is theoretically possible that an agent that affects TLR9 could affect interaction between varicella zoster virus and TLR9. In the opinion of the reviewer, further evaluation of the potential relationship between Heplisav-B and herpes zoster is necessary to better understand this potential risk.*

Drug hypersensitivity: MAEs of drug hypersensitivity were reported by 15 subjects in the Heplisav-B group and 3 subjects in the Engerix-B group. The Applicant reports that in the Heplisav-B group, drug hypersensitivity was reported in response to 12 different drugs [Bactrim (n = 2), Lisinopril (n = 2), Accupril, buproprion, ciprofloxacin, clindamycin, Neosporin, penicillin, Plavix, potassium gluconate, Zithromax Z Pak, and Zoloft). No subjects experienced drug hypersensitivity to more than one drug. The Applicant reports that a review of the subject narratives demonstrates a classic clinical course and response to discontinuing the drug implicated in each case of drug hypersensitivity. The Applicant reports that a similar imbalance was not observed in the other pivotal trials. Lastly, the Applicant proposes that if Heplisav-B were to cause drug hypersensitivity that it would likely occur through a type IV hypersensitivity within 2 to 7 days following exposure with Heplisav-B and the timing of events post-exposure is not consistent with this theory.

Reviewer comment: *All MAEs of drug hypersensitivity were attributed to other medications and none were considered related by investigators. Other hypersensitivities, including seasonal and environmental allergies were more common in Engerix-B subjects compared to Heplisav-B subjects. The reviewer agrees that this is unlikely to represent an increased risk of drug hypersensitivity associated with Heplisav-B.*

The table below shows the events that occurred in at least 0.2% in the Engerix-B group and at least twice the rate of the Heplisav-B group.

Table 28. Number and percent of subjects reporting medically attended events from vaccination through Week 56 in at least 0.2% in the Engerix-B group and at at least twice the rate of the Heplisav-B group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Tooth infection	17 (0.30%)	17 (0.61%)
Exostosis	6 (0.11%)	14 (0.50%)
Actinic keratosis	11 (0.20%)	12 (0.43%)
Haemorrhoids	11 (0.20%)	11 (0.40%)
Eczema	9 (0.16%)	10 (0.36%)
Pyrexia	8 (0.14%)	9 (0.32%)
Otitis externa	9 (0.16%)	9 (0.32%)
Inguinal hernia	5 (0.09%)	8 (0.29%)
Localized infection	8 (0.14%)	8 (0.29%)
Arthropod sting	3 (0.05%)	8 (0.29%)
Ear pain	7 (0.13%)	7 (0.25%)
Folliculitis	6 (0.11%)	7 (0.25%)
Concussion	5 (0.09%)	7 (0.25%)
Glucose tolerance impaired	4 (0.07%)	7 (0.25%)
Musculoskeletal chest pain	7 (0.13%)	7 (0.25%)
Pleurisy	2 (0.04%)	7 (0.25%)
Vertigo positional	3 (0.05%)	6 (0.22%)
Rectal haemorrhage	4 (0.07%)	6 (0.22%)
Eye infection	5 (0.09%)	6 (0.22%)
Upper limb fracture	6 (0.11%)	6 (0.22%)
Hypomagnesemia	2 (0.04%)	6 (0.22%)
Temporomandibular joint syndrome	5 (0.09%)	6 (0.22%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, study DV2-HBV-23, dataset ADAE.
N = number of subjects in each treatment group
n = number of subjects reporting event

Two PTs, tooth infection and exostosis, were reported in at least 0.5% of subjects in the Engerix-B group and at at least twice the rate in the Engerix-B group compared to the Heplisav-B group. In the response to the November 2016 CR comment (item 29) about small observed imbalances in MAEs and SAEs, the Applicant noted nine events that occurred more frequently in the Engerix-B arm that they considered statistically significant (defined as 95% exact CI does not include 1): tooth infection, inguinal hernia, glucose tolerance impaired, exostosis, vertigo positional, arthropod sting, hypomagnesemia, pleurisy, and thyroid neoplasm (0 Heplisav-B recipients, 5 Engerix-B recipients). They noted that these imbalances occurred in events that were reported infrequently and that point estimates for proportions are more imprecise for rare events, which is amplified given the smaller sample size of Engerix-B due to the randomization ratio.

Reviewer comment: *A majority of the preferred terms noted above are not generally considered serious conditions and are relatively common. The possible exception to this assessment is pleurisy and thyroid neoplasm. None of the events of pleurisy was assessed by investigators as serious. There was one additional subject in the Heplisav-B group who reported pleuritic chest pain, which was considered serious. With regard to thyroid neoplasm, by verbatim term, only one of the five subjects has a diagnosis indicative of possible malignancy (verbatim term "cellular aspirate with cytologic atypia of left thyroid"); the others are thyroid nodules. Taking into account the randomization ratio and the established safety record of Engerix-B, it is the assessment of the clinical*

reviewer that the imbalance in all of the events in Table 14 occurred by chance. Furthermore, for some preferred terms, if similar preferred terms, which may represent the same entity, are considered, the imbalance is diminished (for example eczema and dermatitis atopic).

Venous thromboembolism (VTE)

In the integrated safety review of the initial BLA submission in 2012, five subjects who had received Heplisav-B were identified who reported pulmonary embolism (PE), including one fatality in a 46-year-old man without risk factors. The remaining four subjects had at least one risk factor for thrombophilia. No subjects who had received Engerix-B reported pulmonary embolism. SAEs of deep vein thrombosis (DVT) were balanced between the study groups.

As a result, VTE was monitored closely in DV2-HBV-23 and subjects with a qualifying event had further laboratory work-up for genetic risk factors for thrombosis and antiphospholipid antibodies. As only venous, and not arterial, events were previously noted to be imbalanced, the Applicant specified in the protocol and a letter to investigators that only venous thrombotic and thromboembolic events were to be categorized as new-onset thrombotic events and assessed further. In the protocol, DVT and PE are noted as examples; in the CSR thrombophlebitis superficial, venous thrombosis, phlebitis superficial, and thrombosis are also included. One subject was identified by the Applicant who had an MAE of DVT that was misclassified in the datasets as not a VTE. The clinical reviewer identified an additional subject in the datasets who received Heplisav-B and reported an MAE with a preferred term of phlebitis superficial that was not categorized as a VTE. This subject also reported two cerebrovascular accidents (ischemic stroke) while on study. In response to November 2016 CR item 35, in 125428/0.74, the Applicant explained that the investigator mis-categorization the event and consequently the subject was not tested for thrombophilia. Including these events, 12 events of VTE were reported in 12 subjects in the Heplisav-B group (0.21%) and 9 events of VTE were reported in 7 subjects in the Engerix-B group (0.25%). Three Heplisav-B recipients (0.05%) and two Engerix-B recipients (0.07%) reported PE; six Heplisav-B recipients (0.11%) and four Engerix-B recipients (0.14%) reported DVT.

The Applicant reports that all subjects with a VTE had at least one risk factor predisposing them to hypercoagulation, with the exception of one Engerix-B subject. This includes genetic mutations that were identified through study-specified thrombophilia assessments.

In response to CR item 36, in 125428/0.74, the Applicant summarized the results of laboratory evaluations for thrombophilia in subjects with VTE. The Applicant reports that 7 of 11 subjects who received Heplisav-B and 6 of 7 subjects who received Engerix-B who reported thrombotic events had post-event thrombotic laboratory testing performed. Based on the datasets, the reviewer identified four additional subjects in the Heplisav-B group with VTE AEs with testing classified as thrombotic event testing and one additional subject with a VTE (see above), making 11 of 12 Heplisav-B subjects with post-event testing. Three of the Heplisav-B subjects had genetic risk for thrombophilia identified through testing (two heterozygous for the Factor V Leiden mutation and one heterozygous factor II mutation) and a fourth subject had a risk factor identified though medical history (a history of a positive test for factor II mutation about 8 years earlier). Three of the Engerix-B subjects were heterozygous for the Factor V Leiden mutation and

one subject had low Protein C and S activity while on enoxaparin, which should not affect these parameters. Several subjects in both groups had abnormal protein C and/or S activity, but were on warfarin. All subjects tested had normal for anti-beta 2-glycoprotein 1 IgM and IgG and negative anti-cardiolipin IgM and IgG results. Based on the dataset ADLB, the reviewer also identified subjects with abnormal lupus anticoagulant screen, confirmatory, and ratio tests, which can also be affected by anticoagulation.

One subject in the laboratory sub-study also reported a PE. Subject 140-099 was a 65-year-old man with a slightly elevated lupus anticoagulant screen at baseline (42.6 seconds, normal range 27 – 42), normal lupus anticoagulant confirmatory test, elevated baseline prothrombin time (16.9 seconds, normal 9.7 – 12.3), normal PTT, and normal genetic risk factors and anti-phospholipid antibodies. The subject reported an acute myocardial infarction 64 days following the second Heplisav-B injection and was treated with warfarin. At Week 24, the lupus anticoagulant screen increased to 73 seconds, returning to the baseline level (elevated) at the end of the study, and the confirmatory test was elevated at 48.9 seconds (normal range 28-38) and remained elevated. Per the datasets, warfarin was discontinued following this visit and it is unclear what anticoagulation the subject was on. Approximately seven months after the hospitalization for the myocardial infarction and 285 days after the second Heplisav-B injection, the subject experienced SAEs of pulmonary embolus and left ventricular thrombus. In 125428/0.65, the Applicant clarified that this was the subject's first left ventricular thrombus and in 125428.0.74, the Applicant noted the following risk factors for PE in this subject: smoking, hypertension, coronary artery disease, and age. He was treated with warfarin. The thrombotic tests following the pulmonary embolus, showed negative anti-beta 2-glycoprotein 1 and anti-cardiolipin antibodies, and abnormal lupus anticoagulant screen and confirmatory, protein C and protein S, which could be affected by anticoagulation.

Reviewer comment: *In DV2-HBV-23, subjects reporting PE and other VTE events were balanced between treatment groups. The reviewer agrees with the assessment that all subjects who received Heplisav-B and reported VTE had risk factors for hypercoaguability. No clear anti-phospholipid antibodies (anti-beta 2-glycoprotein 1 and anti-cardiolipin antibodies) were identified in any subjects who reported a VTE. Seven of 11 Heplisav-B subjects tested had no identified genetic risk for thrombophilia; one of these subjects (140-099) had baseline abnormalities in clotting assessments and lupus anticoagulant screening test. No subjects that were tested had anti-beta2 glycoprotein 1 or cardiolipin IgM or IgG abnormalities following VTE (see Section 6.3.12.2). Testing was performed after an event of VTE and some thrombotic testing occurred two to three months after an event.*

Please also see the narrative of a subject who received Heplisav-B and reported a VTE that was assessed as related in Section 6.3.12.4.

<u>Renal MAEs</u>

Based upon repeat dose toxicity studies of the adjuvant in rats, showing diffuse proximal tubular degeneration, and limited follow-up periods in DV2-HBV-10 it was recommended that urinalyses, urinary microalbumin studies and serum chemistries be monitored in DV2-HBV-23. In the original integrated summary of safety (ISS), there was one SAE of renal failure identified in the Heplisav-B groups and none in Engerix-B groups.

In DV2-HBV-23, acute renal failure (ARF) MAEs were reported in 18 subjects in the Heplisav-B group (0.32%) and in six subjects in the Engerix-B group (0.22%). Of these subjects, ARF SAEs occurred in four Heplisav-B recipients and three Engerix-B recipients. When broader definitions of acute renal failure are considered, including pre-renal failure, 28 subjects in the Heplisav-B (0.5%) group and 7 subjects in the Engerix-B group (0.3%) reported MAEs with a PT in the SMQ narrow for acute renal failure and 34 subjects in the Heplisav-B (0.6%) group and 12 subjects in the Engerix-B group (0.4%) reported MAEs with a PT in the SMQ broad for acute renal failure subjects in the Heplisav-B (0.6%) group and 12 subjects in the Engerix-B group (0.4%) reported MAEs with a PT in the SMQ for acute renal failure. MAEs with a PT of chronic renal failure were reported by 12 subjects in the Heplisav-B group (0.21%) and three subjects in the Engerix-B group (0.11%). All of the subjects with chronic renal failure, except for one Engerix-B subject, had baseline medical conditions that could predispose to renal failure. Two of the events with a preferred term of chronic renal failure in the Heplisav-B group were SAEs. Fifteen subjects in the Heplisav-B (0.4%) group and 4 subjects in the Engerix-B group (0.1%) reported MAEs with a PT in the SMQ narrow for chronic kidney disease, but 0.8% of both treatment arms reported MAEs with a PT in the SMQ broad for chronic kidney disease.

Please see Section 6.3.12.6 for a discussion of the results of the laboratory sub-study relating to renal function.

Reviewer comment: *In DV2-HBV-23, there may be small imbalances in reports of renal failure between study groups, with more subjects in the Heplisav-B group reporting MAEs and differences diminishing as more similar PTs are considered. Previous studies, as well as DV2-HBV-23, did not identify significant imbalances in between groups in reports of acute or chronic renal failure SAEs. In the judgement of the clinical reviewer there is no clear evidence of an increased risk for renal injury in DV2-HBV-23.*

In the 9 September 2016 IR, CBER requested additional information on subject 130-219 who reported an SAE of "end-stage renal disease" 10 days following dose 2 of Heplisav-B of only seven days duration. In 125428/0.63 and 125428/0.88, the Applicant responded that the subject had a history of chronic kidney disease of unknown cause and was discussing dialysis at the time of study enrollment that was undisclosed to the study site.

Reviewer comment: *Although information is incomplete, the renal failure in this subject appears to be long-standing and not clearly exacerbated by study vaccination.*

6.3.12.3 Deaths

There were 32 deaths in study DV2-HBV-23, 25 in the Heplisav-B group (0.45%) and seven in the Engerix-B (0.25%). Cause of death and timing are presented in the table below. None of the events was assessed as related by the investigators.

Table 29. Fatal adverse events, Safety Population, Study DV2-HBV-23

Age	Sex	Treatment Group Cause of Death SOC Preferred Term	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
		Heplisav-B			

Age	Sex	Treatment Group Cause of Death SOC Preferred Term	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
		Cardiac Disorders			
50	M	Acute coronary syndrome*	1	7	(b) (6)
69	M	Acute myocardial infarction*	2	57	
57	M	Hypertensive heart disease	2	63	
62	M	Hypertensive heart disease*	2	212	
58	F	Hypertensive heart disease	2	225	
70	F	Cardiac arrest	2	243	
47	M	Myocardial infarction	2	287	
55	F	Cardio-respiratory arrest	2	298	
		General			
61	F	Death – Unknown cause	2	59	
51	F	Death – Unknown cause	2	354	
		Hepatobilliary			
68	M	Hepatic cirrhosis	2	27	
		Infectious			
56	M	Hepatitis C	2	35	
		Injury and Poisoning			
58	F	Victim of homicide†	1	1	
49	M	Toxicity to various agents†	2	3	
38	M	Toxicity to various agents†	2	36	
62	M	Overdose†	2	88	
44	M	Toxicity to various agents†	2	159	
49	M	Toxicity to various agents†	2	160	
42	F	Gunshot wound†	2	283	
49	M	Accident†	2	286	
		Neoplasm			
49	M	Lung cancer metastatic	2	244	
43	F	Small cell lung cancer metastatic	2	300	
		Nervous system			
46	F	Hypoxic-ischemic encephalopathy†	2	191	
		Respiratory			
67	M	Acute respiratory failure	2	15	
61	M	Acute respiratory distress syndrome§	2	120	
		Engerix-B			
		Cardiac			
52	M	Myocardial infarction	1	12	
48	M	Hypertensive heart disease‡	3	27	
69	M	Cardio-respiratory arrest	3	88	
		Injury and Poisoning			
44	M	Craniocerebral injury†	1	17	
55	M	Toxicity to various agents†	2	99	
33	F	Head injury†	3	162	
		Neoplasm			

Age	Sex	Treatment Group Cause of Death SOC Preferred Term	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
67	M	Pancreatic carcinoma metastatic	3	179	(b) (6)

Source: Adapted from BLA STN 125428/0.42 CSR DV2-HBV-23, Table 12-3, p. 96
AE: adverse event
SOC: System organ class
* Subject found dead. No autopsy performed.
† Events assessed by the Applicant and reviewer as due to overdose or injury.
‡ Alcohol and drugs contributed.

Nine deaths in the Heplisav-B group and three deaths in the Engerix-B group were considered by the Applicant and the clinical reviewer to be due to drug overdose (not vaccine) or injury based upon the narratives provided, and are noted in the table above. Excluding these deaths, 16 subjects in the Heplisav-B group (0.29%) and four subjects in the Engerix-B group (0.14%) experienced a fatal adverse event. There was one non-injury, non-poisoning death within one month of an active vaccination in the Heplisav-B group, due to acute coronary syndrome, and two in the Engerix-B group, due to myocardial infarction and hypertensive heart disease. There were five non-injury, non-poisoning deaths within 90 days in the Heplisav-B group and three in the Engerix-B group. Deaths due to events in the SOC of cardiac disorders occurred in eight Heplisav-B recipients (0.14%) and three Engerix-B recipients (0.11%).

In the 9 September 2016 IR, the CBER asked the Applicant to provide any additional analyses they conducted to evaluate this imbalance in deaths. In 125428/0.65, the Applicant provided a major adverse cardiovascular events (MACE) analysis, in which the Applicant's consultants performed a blinded adjudication of 10 deaths in the Heplisav-B group and 3 deaths in the Engerix-B group to make a determination of whether they were cardiovascular deaths. Please see Sections 6.3.12.4 and 8.4.2 for a full description of the MACE analysis. In study DV2-HBV-23, three deaths were adjudicated as cardiovascular deaths in the Heplisav-B group and one in the Engerix-B group. Seven additional deaths in the Heplisav-B group were adjudicated as not enough information to make a determination. The two other events that were reviewed in the Engerix-B group were adjudicated as non-cardiovascular deaths.

Brief narratives for deaths of probable or possible cardiac origin, which were reviewed in the MACE analysis, are presented here. The results of the blinded adjudications are also noted.

Subject 130-084 was a 50-year-old man with a relevant medical history of colon cancer, hypertension, dyspnea, mitral valve prolapse and prior mitral valve replacement surgery, chronic obstructive pulmonary disease (COPD), coronary atherosclerosis, cardiomyopathy, left ventricular hypertrophy, and alcohol and cocaine abuse. The only medications he reported taking were cromolyn eye drops, famotidine, and Percocet. He was found dead at home (b) (6) days after his first injection of Heplisav-B with no sign of trauma. The cause of death per the death certificate was "acute coronary syndrome, secondary to atherosclerosis" with cardiomyopathy, left ventricular hypertrophy and alcohol abuse as contributory factors. Autopsy results were unavailable (PT = acute coronary syndrome). Event was adjudicated as cardiovascular death and not an MI.

Subject 131-091 was a 69-year-old man with a relevant medical history of hypertension, edema, chronic renal failure, congestive heart failure, COPD, acute respiratory failure,

supplemental oxygen, abdominal aortic aneurysm, neuropathy, hypertriglyceridemia, and smoking. He was found dead in his home (b) (6) days after his second injection of Heplisav-B. The cause of death listed in the death certificate was acute myocardial infarction due to atherosclerosis. An autopsy was not performed (PT = acute myocardial infarction). Event was adjudicated as undetermined cause of death and not an MI.

Subject 119-318 was a 61-year-old woman with medical history of enlarged heart, depression, and anxiety who died (b) (6) days following dose 2 of Heplisav-B. The Applicant has no information regarding the cause of death. The subject had been considered lost to follow-up. Her death was discovered through the Applicant's reengagement program (PT = death). Event was adjudicated as undetermined cause of death.

Subject 112-311 was a 57-year-old man with hypertension, type 2 diabetes mellitus, diabetic peripheral neuropathy, microalbuminuria, acute kidney injury, and diabetic gastroparesis who was found dead in his home. An autopsy determined that the subject died as a result of hypertensive cardiovascular disease (b) (6) days after his second Heplisav-B injection. Yellow atherosclerotic plaques were seen in the left anterior descending artery. Toxicology testing was positive for alcohol and cyclobenzaprine, but it was determined by the medical examiner this did not contribute to his death (PT = hypertensive heart disease). Event was adjudicated as undetermined cause of death.

Subject 131-049 was a 67-year-old man with aortic stenosis, COPD (on oxygen) and recurrent lung infections for 10 years, and congestive heart failure (CHF), diagnosed 2 months prior to study enrollment. Eleven days after his dose 1 of Heplisav-B, he was hospitalized for one day for a COPD exacerbation. Six days after his second dose of Heplisav-B he was hospitalized for a COPD exacerbation, requiring intubation, mechanical ventilation, and tracheostomy. He then developed methicillin-resistant *Staphylococcus aureus* pneumonia with empyema, and subsequently died from acute respiratory failure due to CHF from severe aortic stenosis (b) (6) days after the second dose of Heplisav-B (PT = acute respiratory failure). Event was adjudicated as non-cardiovascular cause of death.

Subject 132-082 was a 63-year-old man with hypertension and depression who was found dead on the living room floor (b) (6) days after dose 2 of Heplisav-B. An external exam determined the death was due to hypertensive heart disease (PT = hypertensive heart disease). Event was adjudicated as undetermined cause of death.

Subject 138-012 was a 58-year-old woman with medical history of obesity and hypertension who died in her sleep (b) (6) days following dose 2 of Heplisav-B. Autopsy was performed and demonstrated hypertensive cardiovascular disease, focal coronary atherosclerosis, severe pulmonary congestion, cerebrovascular disease with a small lacunar infarct in left basal ganglia, hepatomegaly and macrovesicular steatosis, and glomerulosclerosis. The cause of death was reported as hypertensive cardiovascular disease with (morbid) obesity noted as a contributing factor (PT = hypertensive heart disease). Event was adjudicated as cardiovascular death.

Subject 133-120 was a 71-year-old woman (at the time of death) with obesity, hypertension, type 2 diabetes mellitus, stroke, and high cholesterol, who died from a cardiac arrest (b) (6) days after dose 2 of Heplisav-B. A death certificate reported that the subject died of a cardiac arrest which was due or was a consequence of the subject's

medical history of diabetes. An autopsy was not performed (PT = cardiac arrest). Event was adjudicated as undetermined cause of death.

Subject 122-613 was a 47-year-old man with a relevant medical history of type 2 diabetes, peripheral vascular disease, gangrene left leg, left leg below the knee amputation and right leg edema. (b) (6) days after his second dose of Heplisav-B, the subject experienced a fatal myocardial infarction and died in the hospital. Neither a death certificate nor autopsy results were available (PT = myocardial infarction). Event was adjudicated as undetermined cause of death and unable to determine whether the event was an MI.

Subject 104-152 was a 56-year-old woman with depression and possible alcohol abuse who was found unresponsive at home (b) (6) days after dose 2 of Heplisav-B. She was noted to be pale with bruising on her upper extremities and tracheal deviation. She was transported to an emergency department where she underwent resuscitative efforts that were ultimately unsuccessful. Her final diagnoses included cardiopulmonary arrest, gastrointestinal bleed, and thrombocytopenia. A death certificate was unavailable and an autopsy was not performed (PT = cardiorespiratory arrest). Event was adjudicated as undetermined cause of death.

Subject 119-290 was a 52-year-old woman with a medical history of headaches, depression, anxiety, and insomnia per study records. Additional history of hypertension, bipolar disorder, and heavy smoking was provided in the subject's medical and coroner's records. The subject was found dead (b) (6) days after dose 2 of Heplisav-B, sitting on her couch at home with no signs of foul play, alcohol, or drug abuse. The Applicant reports that the initial report of this event was Death – accidental overdose. The preferred term was changed to Death when it was determined that no autopsy results would be available (PT = death). Event was adjudicated as cardiovascular death.

<u>Engerix-B</u>
Subject 135-070 was a 52-year-old man with a relevant medical history of tobacco and marijuana use who was found down in a parking lot (b) (6) days after his first injection of Engerix-B. Ventricular fibrillation was the initial documented rhythm. He underwent multiple resuscitative efforts. An EKG documented inferior myocardial infarction and troponin was reported as 0.1 (no units or normal range provided). Resuscitative measures were ultimately unsuccessful and he died. Ventricular fibrillation arrest due to acute myocardial infarction was listed as the cause of death. Autopsy demonstrated a remote left ventricular MI, cardiomegaly, and coronary atherosclerosis (45-60% stenosis of left anterior descending and 10-25% of right coronary artery, left circumflex free of significant disease). "It was the opinion of the medical examiner that the subject died of atherosclerotic cardiovascular disease" (PT = myocardial infarction). Event was adjudicated as cardiovascular death and as not an MI.

Reviewer comment: *Two of three adjudicators assessed this event as not an MI, despite a presumed elevation in troponin and EKG changes, albeit after significant resuscitative efforts. As per the Clinical Events Committee Charter, when describing "Type 3: Death, no biomarkers," the document states "Death where symptoms suggestive of myocardial ischemia are present and with (presumed) new ischemic or new LBBB on ECG, but where death occurs before cardiac biomarkers can be obtained or could rise or (in rare cases) were not collected. Note: For this study, these will be classified as CV deaths." Thus, this subject was adjudicated as a CV death, not a*

myocardial infarction. It is possible that the subject had myocardial damage due to an arrhythmia, as a result of an old myocardial infarction, not directly due to coronary artery disease.

Subject 119-175 was a 48-year-old man with a medical history of hypertension, gout, and alcohol abuse who was found dead in the bed of a motel room. An empty beer can and an empty pint of vodka were found on the floor, as well as signs of tobacco and possible marijuana use. No autopsy was performed but a chest x-ray was consistent with pulmonary edema. Toxicology results included blood ethanol 0.32 gm/dL, vitreous ethanol 0.45 gm/dL, and other drugs of abuse including cocaine, hydrocodone, and codeine. The coroner determined the cause of death to be hypertensive heart disease with contributory factors of cocaine, heroin, and ethanol use (PT = hypertensive heart disease). Event was adjudicated as a non-cardiovascular death.

Reviewer comment: *This event is suspicious for alcohol poisoning, as well as cocaine and opioids, contributing to, if not causing death.*

Subject 130-392 was a 70-year-old man with relevant medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, patent foramen ovale, congestive heart failure, transient ischemic attack, anemia, and COPD (diagnosed on-study) who reported a cough, progressing to weakness, nausea, and vomiting, for which he was admitted. He had a bandemia of 25. Shortly after admission, he was found unresponsive. During the hospitalization, he was diagnosed with aspiration pneumonia, cerebrovascular accident, sepsis, acute renal failure, and gastrointestinal bleed. He was eventually transferred to a nursing home, where he was found unresponsive while eating dinner in cardiopulmonary arrest and died (PT = cardiorespiratory arrest). The cause of death per the death certificate was cardiorespiratory arrest due to chronic respiratory failure due to a cerebrovascular accident. No autopsy was performed. Event was adjudicated as non-cardiovascular death, but the subject was also adjudicated as having a stroke.

Reviewer comment: *The rate of death due to causes other than injury and illicit drug overdose in the Heplisav-B group is twice the rate in the Engerix-B group. Narratives of these events indicate significant baseline disease in these subjects. There does not appear to be a clear excess of deaths within the Heplisav-B group that are closely temporally associated with vaccination. However, a difference in mortality may be concerning because 1) the study was randomized and an analysis of baseline medical characteristics demonstrates similar baseline conditions and cardiac risk factors between groups, 2) of the imbalance also noted in myocardial infarctions (see Section 6.3.2.4), and 3) the Applicant's post-hoc blinded adjudication shows an imbalance in deaths that did not have enough information to determine a cause of death.*

The information regarding many of these deaths is very limited. The clinical reviewer agrees that the results of the blinded adjudications of events are reasonable. There were seven subjects in the Heplisav-B group and no subjects in the Engerix-B group with an undetermined cause of death. Most of these subjects were found dead, but as they were last seen alive more than 24 hours previously, they were categorized as unknown cause of death, consistent with the instructions to adjudicators (125428/0.65) and standardized definitions.[31] *The most likely cause of sudden death in the absence of evidence of other causes (for example, other major or terminal medical conditions, illicit drug use, foul play) is cardiac. In the opinion of the clinical reviewer it is also reasonable*

to consider most of these deaths to be cardiac in nature. Presuming unknown causes of death to be cardiac deaths is also consistent with common analytic approaches.[31]

6.3.12.4 Nonfatal Serious Adverse Events

Overall, SAEs were reported in 345 Heplisav-B subjects (6.2%) and 148 Engerix-B subjects (5.3%). Three hundred twenty-five Heplisav-B subjects (5.8%) reported 491 non-fatal SAEs and 142 Engerix-B subjects (5.1%) reported 212 non-fatal SAEs.

The most commonly reported SAEs, including fatalities, for the Heplisav-B group from vaccination through Week 56 are presented in the table below.

Table 30. Number and percentage of subjects reporting the most commonly reported treatment-emergent SAEs (≥ 4 subjects) from vaccination through Week 56 in the Heplisav-B group, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Pneumonia	15 (0.27)	8 (0.29)
Acute myocardial infarction	14 (0.25)	1 (0.04)
Non-cardiac chest pain	9 (0.16)	7 (0.25)
Chronic obstructive pulmonary disease	9 (0.16)	3 (0.11)
Cellulitis	7 (0.13)	4 (0.14)
Osteoarthritis	7 (0.13)	3 (0.11)
Cerebrovascular accident	7 (0.13)	3 (0.11)
Atrial fibrillation	6 (0.11)	3 (0.11)
Cardiac congestive failure	6 (0.11)	3 (0.11)
Coronary artery disease	6 (0.11)	2 (0.07)
Small intestinal obstruction	6 (0.11)	2 (0.07)
Acute respiratory failure	6 (0.11)	1 (0.04)
Cholecystitis	5 (0.09)	2 (0.07)
Sepsis	5 (0.09)	1 (0.04)
Toxicity to various agents	5 (0.09)	1 (0.04)
Diabetic ketoacidosis	5 (0.09)	1 (0.04)
Depression	5 (0.09)	1 (0.04)
Asthma	5 (0.09)	1 (0.04)
Hypertension	5 (0.09)	3 (0.11)
Hypertensive heart disease	4 (0.07)	1 (0.04)
Cholelithiasis	4 (0.07)	4 (0.14)
Gastroenteritis	4 (0.07)	1 (0.04)
Urosepsis	4 (0.07)	2 (0.07)
Convulsion	4 (0.07)	1 (0.04)
Transient ischemic attack	4 (0.07)	1 (0.04)
Bipolar I disorder	4 (0.07)	0
Calculus ureteric	4 (0.07)	2 (0.07)
Renal failure acute	4 (0.07)	3 (0.11)
Pneumothorax	4 (0.07)	1 (0.04)
Deep vein thrombosis	4 (0.07)	3 (0.11)

Source: Adapted from BLA STN 125428/0.042, CSR DV2-HBV-23, Table 12-14, p. 97.
The table differs from the table presented in the CSR, in that only treatment-emergent events are included here.
N = number of subjects in each treatment group

n = number of subjects reporting event

Treatment-emergent SAEs reported in at least 0.05% of subjects in the Heplisav-B group (three subjects) and at at least twice the rate of the Engerix-B group were: acute myocardial infarction (0.25% Heplisav-B, 0.04% Engerix-B), bipolar 1 disorder (0.07% Heplisav-B, 0 Engerix-B), acute respiratory failure (0.11% Heplisav-B, 0.04% Engerix-B), depression and depression suicidal (0.11% Heplisav-B, 0.04% Engerix-B), sepsis (0.09% Heplisav-B, 0.04% Engerix-B), toxicity to various agents (0.09% Heplisav-B, 0.04% Engerix-B), diabetic ketoacidosis (0.09% Heplisav-B, 0.04% Engerix-B), asthma (0.09% Heplisav-B, 0.04% Engerix-B), cardiac arrest (0.05% Heplisav-B, 0 Engerix-B), bronchitis (0.05% Heplisav-B, 0 Engerix-B), and gunshot wound (0.05% Heplisav-B, 0 Engerix-B). When acute respiratory failure is considered with respiratory failure and respiratory arrest, SAE rates are similar between groups (0.13% Heplisav-B, 0.14% Engerix-B). Small imbalances in several of these SAEs are discussed here and the imbalance in cardiac SAEs is discussed in more detail below.

Reviewer comment: *In the second review cycle, in the judgement of the clinical reviewer, the following numerical imbalances in SAEs were potentially clinically significant and warranted additional information from the Applicant: bipolar disorder, depression, sepsis, and diabetic ketoacidosis. For some of these events, numerical imbalances in MAEs were also noted and are discussed here. Please also see the discussion of asthma under temporally related events.*

In the 10 November 2016 CR, item 29, the Applicant was asked to discuss small imbalances unfavorable to Heplisav-B in specific SAEs and MAES. The following is a summary of the differences noted and the Applicant's discussion of these small imbalances, submitted in 125428/0.74:

- Bipolar and Bipolar I (MAEs and SAEs): MAEs with the MedDRA Higher Level Term (HLT) of Bipolar disorder were reported in 15 Heplisav-B recipients (0.3%) and 2 Engerix-B recipients (0.1%). SAEs of Bipolar disorder by HLT were reported in seven Heplisav-B recipients (0.1%) and one Engerix-B recipient (0.04%). Prior to study enrollment, rates of medical histories of bipolar and bipolar 1 disorder (2.5% Heplisav-B, 2.2% Engerix-B), depression and major depression (17.4% Heplisav-B, 17.6% Engerix-B), and any history in the system organ class (SOC) of psychiatric disorders (30.9% Heplisav-B, 31.8% Engerix-B), were similar between groups.

  The Applicant reports that three subjects in the Heplisav-B group and no subjects in the Engerix-B group reported bipolar disorder within 42 days of the last active dose; all subjects had a prior history of bipolar disorder and one had discontinued his medications. The Applicant reports that of subjects who reported MAEs of bipolar disorder, six subjects in the Heplisav-B group and one subject in the Engerix-B group had no prior history of bipolar disease. Only one subject without a prior history of bipolar disorder in the Heplisav-B group was assessed as having an SAE of bipolar disorder. Of presumed cases of new-onset bipolar disorders, day of onset ranged from 55 to 344 days (median 120 days) following last active dose in the Heplisav-B group and at day 162 in the Engerix-B group.

  No events of bipolar disorder were reported in DV2-HBV-10, and one event was reported by a subject who received Heplisav-B in DV2-HBV-16. While the clinical reviewer has identified reports of elevated expression of TLRs, including

TLR9, in peripheral blood mononuclear cells in subjects with depression,[32] the Applicant notes no known role of TLR9 in bipolar disorder based on hypotheses of bipolar disorder pathophysiology and notes that CpG does not cross the blood-brain barrier.

- Depression: Six Heplisav-B recipients and one Engerix-B recipient reported SAEs with a HLT of depressive disorders. All subjects who reported these SAEs had a history of depression. Four Heplisav-B recipients had a documented precipitating event. The Applicant noted no temporal association and no biologically plausible mechanism.

- Sepsis: SAEs of sepsis were reported by five Heplisav-B recipients and one Engerix-B recipient. The Applicant reports that each SAE of sepsis in the Heplisav-B group was secondary to an infectious source; the event of sepsis in the Engerix-B group had an unknown source. The Applicant reports no known biological plausibility for a relationship between Heplisav-B and these events of sepsis and notes that they followed a variety of infectious etiologies. The clinical reviewer further notes that SAEs in the SOC of infections and infestations were not imbalanced between groups.

- Diabetic ketoacidosis (DKA): SAEs of DKA were reported in five Heplisav-B recipients and one Engerix-B recipient. The Applicant reports that, in the Heplisav-B group, two subjects had discontinued their medications and two subjects had new-onset type 2 diabetes who presented in DKA. The one Engerix-B recipient had new onset type 2 diabetes who presented in DKA. The Applicant notes that all events happened more than two months from last active injection and that they did not identify a biologically plausible mechanism. The clinical reviewer further notes that the SMQ narrow for hyperglycemia/new onset diabetes mellitus was balanced between treatment groups in SAEs (0.14% Heplisav-B, 0.11% Engerix-B), as well as MAEs (2.0% Heplisav-B, 2.1% Engerix-B).

Reviewer comment: *For many of these events, simply because a biologically plausible mechanism may not be known, does not necessarily mean that there is not such a mechanism. However, given the additional information provided by the Applicant, the reviewer agrees that the differences in events of bipolar, depression, sepsis, and DKA are not large and are unlikely to represent safety signals.*

In an analysis of SAEs by SMQ, a standardized query for grouping terms, the following differences between treatment group were identified with RRs > 3: Breast neoplasms, malignant (6 Heplisav-B subjects, 0.11%; 0 Engerix-B), gastrointestinal non-specific inflammation (5 Heplisav-B subjects, 0.09%; 0 Engerix-B), non-infectious encephalopathy (4 Heplisav-B subjects 0.07%; 0 Engerix-B), shock (7 Heplisav-B subjects, 0.13%; 1 Engerix-B subject, 0.04%), MI (19 Heplisav-B subjects, 0.34%; 3 Engerix-B subjects, 0.11%); and arthritis, ventricular tachyarrythmias, edema/effusions/fluid overload, hyponatremia/syndrome of inappropriate antidiuretic hormone secretion, and gastrointestinal pre-malignant disorders, each reported in 3 Heplisav-B subjects (0.05%) and 0 Engerix-B subjects. Please see the discussion below regarding SAEs of MI. Gastrointestinal inflammation and non-infectious encephalopathy SMQs include varied preferred terms with different etiologies. Of the subjects with shock

in the Heplisav-B arm, six of seven events were cardiac in nature and are discussed either with cardiac SAEs below, or in Section 6.3.12.3 (deaths), as appropriate.

Malignant breast neoplasm SAEs were reported in six Heplisav-B recipients and no Engerix-B recipients and one additional Heplisav-B recipient reported a non-serious breast malignancy. Percentage of subjects reporting SAEs and MAEs in the SOC of neoplasms, which includes benign and malignant neoplasms, were similar between treatment groups (SAEs reported in 0.6% of Heplisav-B recipients and 0.5% of Engerix-B recipients). Other solid organ malignant tumor SAEs were reported in a greater percentage of Engerix-B recipients. For example, ovarian malignant tumors were reported in no Heplisav-B recipients and two Engerix-B recipients (0.07%) and prostate malignant tumors were reported in four Heplisav-B recipients (0.07%) and four Engerix-B recipients (0.14%). In study DV2-HBV-10, breast cancer (by HLT) was reported in three Heplisav-B recipients (0.2%) and no Engerix-B recipients and in DV2-HBV-16, in two Heplisav-B (0.1%) and two Engerix-B recipients (0.4%). Of the 12 breast cancers that were identified in the Heplisav-B group in three pivotal trials, 9 were reported within 6 months following vaccination, including 2 within the first month of the study.

The evidence of a relationship between TLR9 and breast cancer is complex.[33, 34] TLR9 mRNA and protein are expressed on breast cancer cell lines and in clinical breast cancer specimens, and breast cancer cells expressing TLR9 have been shown to enhance invasive capability. However, TLR9 is a positive prognostic indicator in triple negative (estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 negative) breast cancer and in other tumors (neuroblastoma), TLR9 has been shown to enhance apoptosis and decrease proliferation. Furthermore, TLR9 has also been shown to increase invasiveness of ovarian cancers and has been suggested to play a role in early prostate cancer development, both of which were reported in greater proportions in the Engerix-B group. Please also see Section 8.4.2 for a discussion of prostate cancers in other studies.

Reviewer comments: *For most events identified by the SMQ analysis, SAEs were infrequent and represented different etiologies, so as not to suggest a safety signal. MI was a safety signal that warranted further analysis and is discussed below. Whether there is an association between breast cancer and Heplisav-B is unclear, but the occurrence of breast cancer in both treatment groups in study DV2-HBV-16 and the occurrence of other cancers at higher rate in the Engerix-B group suggest the breast cancer findings are by chance. Furthermore, given the timing of event onset, it seems less likely that the vaccine would so rapidly contribute to an increase in breast cancer, given the long time required for cancer to develop.*

SAEs were evaluated by temporal association with vaccination. The table below shows the SAEs that were reported in at least two subjects in either group within 30 days of vaccination.

Table 31. Reviewer-generated analysis of the number and percentage of subjects reporting treatment-emergent SAEs within 30 days of vaccination, for events with at least two subjects reporting in one treatment group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Chronic obstructive pulmonary disease	4 (0.07)	0
Asthma	3 (0.05)	0
Acute respiratory failure	2 (0.04)	0
Anemia	2 (0.04)	0
Atrial fibrillation	2 (0.04)	0
Bronchitis	2 (0.04)	0
Cellulitis	2 (0.04)	0
Cerebrovascular accident	2 (0.04)	0
Non-cardiac chest pain	2 (0.04)	0
Suicide attempt	2 (0.04)	0
Cholelithiasis	0	2 (0.07)
Deep vein thrombosis	0	2 (0.07)

Source: Reviewer-generated based on BLA STN 125428/0.042, dataset ADAE.
N = number of subjects in each treatment group
n = number of subjects reporting event

The respiratory events are discussed in greater detail here. There is overlap between several subjects reporting PTs that are displayed in the table above, however an imbalance is still noted in acute respiratory SAEs within 30 days of the last active vaccination. If you consider COPD, asthma and bronchitis SAEs, six subjects in the Heplisav-B group reported such events and none in the Engerix-B group. All subjects had a history of either COPD or asthma. Two subjects reported these events within one week of vaccination, both with significant comorbidities. One subject (131-049) reported two events of COPD, the second SAE ultimately leading to pneumonia, the acute respiratory failure SAE in the table above, and death (see Section 6.3.12.3). The second subject (105-314) had multiple medical problems, which included a history of congestive heart failure (CHF) with an ejection fraction of 15-20%, and an admission for acute on chronic CHF with pulmonary edema three days before the first vaccination (information submitted in 125428/0.63 in response to the 9 September 2016 IR). One more subject reported asthma and bronchitis SAEs starting within 1-2 weeks following vaccination. The remainder of subjects reported these events greater than two weeks following vaccination. One of these subjects was on oxygen at baseline. The second acute respiratory failure in the table above (130-094) was due to CHF per the narrative.

Reviewer comment: *There appears to be an imbalance in acute obstructive respiratory SAEs occurring within one month after vaccination, with six Heplisav-B recipients and no Engerix-B recipients reporting these events. All subjects had prior respiratory disease, with some having quite significant disease, including the two subjects who reported events within one week of vaccination. Throughout the study period, there was a numerical imbalance in asthma SAEs (by SMQ narrow for asthma/bronchospasm) (0.09% Heplisav-B, 0.04% Engerix-B) and COPD SAEs (0.16% Heplisav-B, 0.11% Engerix-B), but MAEs for both were balanced between treatment groups. If a vaccine induced a hypersensitivity reaction of bronchospasm, one would generally expect an increase in events with a very short interval between vaccination and event onset, for example within one week. TLR signaling pathways culminate in activation of NF-κB and NF-κB activation is implicated in chronic inflammatory diseases, such as chronic obstructive pulmonary disease, and asthma.*[35] *Given the imbalance observed, the*

clinical reviewer cannot rule out a causal relationship in subjects that may be pre-disposed to respiratory illness.

Also of note from the table above, the two SAEs of anemia had plausible causes other than vaccination: dysfunctional uterine bleeding in one subject and stab wounds in another. Please see the discussion below for additional details regarding the events of atrial fibrillation and cerebrovascular accidents.

Related SAEs: Four SAEs in three subjects in the Heplisav-B group (0.05%) were assessed as related by investigators: one pregnant subject with intrauterine growth restriction in two twin infants and Ebstein's anomaly in one twin (see Section 9.1), electrophoresis protein abnormal, and DVT. Four SAEs in four subjects in the Engerix-B group (0.14%) were assessed as related by investigators: Ebstein's anomaly, complex partial seizures, pulmonary embolism, and DVT. The narrative for the two non-pregnancy related SAEs follows. The narratives for the pregnancy related SAEs are in Section 9.1.1.

Subject 117-125 was a 67-year-old man with a past medical history of COPD, emphysema, basal cell carcinoma, umbilical hernia, rosacea, and osteoarthritis of the right hand. Approximately three months after the second dose of Heplisav-B, he reported "throbbing of the hands," which is reported as resolved one month later. The subject had an abnormal serum protein electrophoresis nine months after the second dose of Heplisav-B. Abnormal results included immunoglobulins 2.1 g/dL (reference range 0.5 - 1.4 g/dL), IgG 1460 mg/dL (reference range 653 – 1310 mg/dL), and IgM 1140 mg/dL (reference range 57 – 230 mg/dL). The subject's laboratory results included normal values for alpha 1 globulin, alpha 2 globulin, beta globulin, IgA, and albumin. Laboratory notes reported that the "M-protein concentration was 0.93 g/dL, unchanged since [3 months previously]" and "quantitative immunoglobulins were essentially unchanged since last measured [4 months previously]." Hematocrit of 37.8% (normal 42-54) and monocytes 19.3% (2-11) were also noted. It was unclear why the serum protein electrophoresis was obtained. It was discovered the subject had been participating in an observational trial of COPD. Per the subject, there was no study medication administered; only x-rays and lab work were obtained. The subject informed the site that the throbbing in hands was due to "protein in blood." No other MAEs are reported aside from a lipoma and lipoma removal. No final diagnosis, end date, or outcome was provided. The site made multiple attempts to obtain source documents without success. The narrative stated the subject was to have additional follow-up, but the site reported that they were unable to obtain this information after multiple attempts, in 125428/0.74 in response to 10 November 2016 CR item 38.

Reviewer comment: *The subject has an M-protein, elevated IgG and IgM, anemia, and a monocytosis. There are two subjects who reported multiple myeloma following vaccination (one SAE) and two additional subjects who reported monoclonal gammopathy of undetermined significance (MGUS) in the Heplisav-B group. No subjects in the Engerix-B group reported these events. The annual incidence of MGUS in men and women at age 50 is estimated to be 120 per 100,000 and 60 per 100,000 population, respectively.[36] Therefore 2-3 reports would not be unexpected in this population. The annual incidence of multiple myeloma in the U.S. is approximately 4 to 5 per 100,000 (0.004%). Two reports is somewhat higher than might be expected in this population (2/5587 = 0.04%).[37] There is a numerical imbalance in events of multiple*

myeloma. The number of events is small and it is difficult to draw definitive conclusions regarding relationship to vaccine.

Subject 126-234 was a 46-year-old African-American woman with a relevant medical history of a basilar artery clot seven years prior (reported in hospital notes). The subject was hospitalized 72 days after receiving the second dose of study vaccine after having experienced a syncopal episode followed by slurred speech. Evaluation by CT and MRI demonstrated that the subject had an acute cerebellar stroke. She was treated with a heparin drip and bridging to warfarin. During hospitalization she complained of right upper extremity pain. A B-mode ultrasound at that time showed a free floating clot in the internal jugular vein while being on a heparin drip. Lifelong anticoagulation at INR > 2.5 was recommended. Five days later, she was diagnosed with an acute deep vein thrombosis in the right internal jugular vein and an acute superficial venous thrombosis in the right proximal basilic veins. Factor V Leiden testing was negative. The narrative states that during the hospital course coagulation profile was negative except for deficiencies in proteins C and S, which would be expected in the setting of anticoagulation. The investigator assessed the stroke as serious and as not related to the study vaccine. The investigator assessed the deep vein thrombosis as serious and as possibly related to the study vaccine. Thrombophilia assessment performed three months later, while the subject was on warfarin, showed mildly elevated lupus anticoagulant (screening and confirmatory) and low protein C and S activity.

Reviewer comment: *The subject reported multiple thrombotic events approximately two months following vaccination. However, she also has a history of a prior basilar artery clot that was not recorded in her study medical history. Lupus anticoagulant can be affected by warfarin. It is not clear what one abnormal test indicates in this subject. Other antiphospholipid antibody testing was negative three months following the event. Two SAEs and one MAE of VTE reported in subjects in the Engerix-B group were assessed by investigators as possibly related and thrombotic events were balanced in the two treatment groups.*

Other SAEs: Additional information for subject 102-046 who reported only one AE, a serious event of diaphragmatic paralysis, treated with 30 days of oral steroids, was requested in the November 2016 CR. The Applicant submitted information in 125428/0.74 that demonstrated the subject was admitted for dyspnea and hypoxemia that was thought by treating physicians to be multifactorial, specifically due to under-treatment of sleep apnea and diaphragmatic paralysis of unclear etiology. MRI of the brain and cervical spine, showed no pathology of the cervical cord or brainstem. A phrenic nerve stimulation and diaphragm biopsy was recommended as an outpatient.

Reviewer comment: *This CR item (38f) was adequately addressed. The etiology of the event is unclear.*

Cardiac SAEs
While rates of non-serious MAEs in the SOC of cardiac disorders was similar between treatment groups (1.22% Heplisav-B, 1.19% Engerix-B), as reported by the Applicant in the response to the September 9, 2016 IR, rates of cardiac SAEs were more frequent in the Heplisav-B group compared to the Engerix-B group (0.9% Heplisav-B, 0.5% Engerix-B). This imbalance was most notable in SAEs of acute myocardial infarction (AMI), reported in 14 subjects in the Heplisav-B group (0.25%) and one subject in the Engerix-B group (0.04%). An overview of all cardiac SAEs is shown in the table below.

Table 32. Number and proportion of subjects with treatment-emergent serious adverse events in the system organ class of cardiac disorders by treatment group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	14 (0.25)	1 (0.04)
Angina pectoris	2 (0.04)	1 (0.04)
Angina unstable	1 (0.02)	0
Atrial fibrillation	6 (0.11)	3 (0.11)
Atrial flutter	2 (0.04)	1 (0.04)
Bradycardia	2 (0.04)	0
Cardiac arrest	3 (0.05)	0
Cardiac failure	2* (0.04)	0
Cardiac failure acute	1 (0.02)	0
Cardiac failure congestive	6* (0.11)	3 (0.11)
Cardiac ventricular thrombosis	1 (0.02)	1 (0.04)
Cardiogenic shock	1 (0.02)	0
Cardiomyopathy	0	1 (0.04)
Cardio-respiratory arrest	1 (0.02)	1 (0.04)
Coronary artery disease	6 (0.11)	2 (0.07)
Coronary artery occlusion	1 (0.02)	1 (0.04)
Coronary artery stenosis	2 (0.04)	0
Hypertensive heart disease	4 (0.07)	1 (0.04)
Myocardial infarction	2 (0.04)	1 (0.04)
Myocardial ischemia	1 (0.02)	0
Pulseless electrical activity	1 (0.02)	0
Supraventricular tachycardia	1 (0.02)	0
Ventricular fibrillation	1 (0.02)	0
Ventricular tachycardia	2 (0.04)	0
Total Subjects with at least 1 Cardiac SAE	**51 (0.91)**	**15 (0.54)**

Source: Adapted from BLA STN 125428/0.42, CSR DV2-HBV-23, Table 12-16, p. 105.
N = number of subjects in each treatment group
n = number of subjects reporting event
* Absolute subject numbers for cardiac failure and cardiac failure congestive were incorrect in the VRBPAC briefing document issued for the 28 July 2017 VRBPAC; correct percentages were listed. This table contains the correct numbers.

Myocardial Infarction Cardiac SAEs: The Applicant presented an analysis of all events in the SMQ narrow for myocardial infarction (MI), in an effort to group events which are likely to represent AMI, but may have been mapped to a different PT. The table below summarizes the SAEs in this SMQ reported in DV2-HBV-23.

Table 33. Number of subjects with treatment-emergent myocardial infarction serious adverse events (MedDRA SMQ Narrow) by treatment group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n	Engerix-B N = 2781 n

Preferred Term	Heplisav-B N = 5587 n	Engerix-B N = 2781 n
Acute coronary syndrome	1	0
Acute myocardial infarction	14	1
Angina unstable	1	0
Coronary artery occlusion	1	1
Myocardial infarction	2	1
Total Subjects with at least one event	19 (0.34%)	3 (0.11%)

Source: Adapted from BLA STN 125428/0.42, CSR DV2-HBV-23, Table 12-17, p. 106.
N = number of subjects in each treatment group
n = number of subjects reporting event

When SAEs with a PT in the SMQ Narrow for MI are considered, an imbalance in events persists (0.3% Heplisav-B, 0.1% Engerix-B, RR = 3.15, 95% Wald CI 0.93, 10.64; 95% Koopman score CI 1.00,9.98). The imbalance between treatment groups is observed only with the PT AMI.

As a preliminary method of evaluating adverse events, the reviewer examined the relative risk and asymptotic confidence intervals surrounding events. The PT of AMI (SAEs) has the highest relative risk and lower bound of the 95% CI of all individual PTs reported in DV2-HBV-23. AMI is in the narrow SMQ of ischemic heart disease (level 1), and myocardial infarction (level 2). Several other narrow SMQs (SAEs) have greater relative risks, than that for ischemic heart disease and myocardial infarction. But these are events that are fewer in number (3 – 7 subjects in the Heplisav-B group compared to 0 – 1 events in the Engerix-B group). The narrow SMQs for SAEs with the highest lower bound of the 95% asymptotic CI were, in descending order: ischemic heart disease, which includes the SMQ of MI and other non-infarct ischemic cardiac SAEs, such as coronary artery disease (RR = 2.89, 95% asymptotic CI 1.12, 7.45); myocardial infarction/ischemic heart disease (see above); and embolic and thrombotic events/ arterial, which includes myocardial infarctions (RR = 2.39, 95% 0.91, 6.26); ischemic cerebrovascular conditions (RR = 1.89, 95% CI 0.71, 5.06); and accidents (RR = 1.44, 95% CI 0.71, 2.96). Based on the SMQ of ischemic heart disease, there was also a numerical imbalance in SAEs of cardiac ischemia, which did not lead to infarct, with 10 subjects in the Heplisav-B group (0.18%) and 2 subjects in the Engerix-B group (0.07%) reporting such events.

Reviewer comment: *An imbalance in myocardial infarctions was observed that persisted when other PTs that were likely to also describe myocardial infarctions were included. The upper and lower bound of the confidence interval were high, indicating a greater risk in the Heplisav-B arm. Combining other ischemic cardiac events demonstrated numerical imbalances in the same direction, albeit of a lesser magnitude. For these reasons and because of the potential clinical significance if myocardial infarction were associated with vaccination, CBER thought these events warranted further assessment. The CIs listed above were used as preliminary tools to identify events that may need further evaluation. As the study was not designed to assess these RRs, the CIs should not be used to rule in or out statistical significance. Furthermore, while the Wald CI was used as a preliminary tool, the statistical reviewers endorsed the Koopman score confidence interval to calculate confidence intervals around the relative risk of the cardiovascular events in this study. These CIs are given below, where appropriate.*

In the 9 September IR and the 10 November 2016 CR letter, CBER requested further analyses of MI, as well as narratives and CRFs for all cardiovascular SAEs, which had not been submitted in the 16 March 2016 CR response.

As part of their analyses of cardiovascular events, submitted in 125428/0.65 in response to the 9 September 2016 IR, the Applicant performed a major adverse cardiovascular events (MACE) analysis on the three pivotal trials. The results of the MACE analysis for studies DV2-HBV-10 and -16 are described in Section 8.4.2. The Applicant obtained independent, blinded, post-hoc, adjudication of SAEs of cardiovascular (CV) death, MI, and stroke by external consultants. For CV death and MI, two cardiologists categorized events as 1) a MACE event, 2) not a MACE event, or 3) insufficient information to make a determination. If the first two consultants disagreed, a third consultant was used. For stroke, one neurologist reviewed cases and adjudication was final. The composite three-point MACE outcome included SAEs adjudicated as 1) cardiovascular death, 2) MI (non-fatal), and 3) stroke (non-fatal). Analyses in this section are based on events identified by PT as in the SMQ narrow for MI, unless otherwise stated. Preferred terms selected to identify potential MACE outcomes were chosen in a blinded manner by another external consultant.

CBER obtained expert consultations from three cardiologists for assistance with evaluating the imbalance in events of MI observed in study DV2-HBV-23. Input from the cardiologists will be included in the discussion and is also summarized in Section 5.4.2. Please see the full consults in Appendix B.

Reviewer comment: *All the consultants agreed that, overall, the Applicant had conducted a reasonable post-hoc analysis of cardiovascular events, while adding critiques regarding certain aspects of the analysis. Overall, the clinical reviewer agrees. It is the opinion of the clinical reviewer that the choice of PTs to identify events for adjudication had the potential to miss some SAEs of MI that were reported or coded differently. For example, coronary artery occlusion and unstable angina, which are in the narrow SMQ for MI, were not PTs selected for adjudication. SAEs of cardiac failure and cardiac arrest were not reviewed for adjudication as MIs, despite MI being a primary cause of each. However, in DV2-HBV-23, upon the review of the SAE narratives, no additional events of MI, with evidence of myocardial necrosis and troponin elevation, were identified. Please see Section 8.4.2 for a discussion of this issue in the other pivotal studies.*

Brief narratives for the events with a PT in the narrow SMQ for MI, which includes all events that were reviewed as potential MIs by the Applicant's adjudicators, are presented here based upon narratives provided by the Applicant. Final results of the Applicant's external adjudications are also presented. Narratives of deaths due to MI are presented in Section 6.3.12.3 (subjects 130-084, 131-091, 122-613, 135-070).

<u>Heplisav-B</u>
Subject 141-110 was a 61-year-old woman with a relevant medical history of chest pain and hypertension who experienced a non-ST elevation myocardial infarction two days after the second injection of Heplisav-B, which was confirmed by cardiac catheterization (PT = acute myocardial infarction). The narratives and datasets conflict with respect to whether the subject had a prior history of coronary artery disease (CAD), with the narrative stating that it was unknown if she had such a history. The datasets also state

she had a six-year history of hypertriglyceridemia; she was not on treatment at baseline and triglycerides were 147 at the time of the event. The event was adjudicated as an MI.

Subject 106-312 was a 65-year-old woman with a relevant medical history of type 2 diabetes, dyslipidemia, hypertension, heart palpitations, Cushing's syndrome, and sleep apnea. Twenty-four days following dose 1 of Heplisav-B she was seen by a cardiologist for three days of worsening heart palpitations and was prescribed isosorbide mononitrate. A percutaneous coronary intervention was attempted on an unknown date in the same month as dose 2, but was unsuccessful. The subject discontinued the isosorbide mononitrate due to side effects. Three weeks following dose 2 she informed the site she was scheduled for cardiac catheterization. Five weeks after dose 2, a cardiac nuclear perfusion scan performed showed ischemic changes. She underwent a cardiac catheterization, which demonstrated multi-vessel coronary artery disease and total occlusion of her third obtuse marginal artery. Four cardiac stents were placed. The Applicant conservatively considers the onset of this event to be 14 days after the first injection of Heplisav-B as the date of the first catheterization is unknown (PT = coronary artery occlusion). The event was not selected for adjudication based on the PT.

Reviewer comment: *While there was no reported evidence of infarct (no EKG changes or troponins were provided), the event represents a coronary ischemic event in close temporal association with Heplisav-B.*

Subject 113-011 was a 68-year-old woman with a relevant medical history of COPD, hyperlipidemia, and tobacco use who reported an inferior myocardial infarction, followed by non-sustained ventricular tachycardia 51 days following the second dose of Heplisav-B (PT = myocardial infarction). The narratives and datasets conflict over whether the subject had a prior history of coronary artery disease (CAD). The CRFs state that the subject's CAD was undiagnosed prior to the event. The event was adjudicated as an MI.

Subject 134-373 was a 64-year-old man with a relevant medical history of hyperlipidemia, hypertension, and tobacco use who reported an ST elevation myocardial infarction 61 days after his second injection of Heplisav-B. A cardiac catheterization was performed with angioplasty and three drug-eluting stents placed in the left anterior descending artery (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 112-090 was a 53-year-old man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes (diet-controlled), morbid obesity, sleep apnea, multiple prior abdominal surgeries, and alcoholism. He was admitted to the hospital with abdominal pain, diarrhea, a partial small bowl obstruction, and acute kidney injury due to dehydration and diarrhea. He was treated medically and improved. On hospital day 3, he experienced a non-ST elevation myocardial infarction 63 days after his second injection of Heplisav-B. A cardiac catheterization showed multi-vessel disease and three stents were placed (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 140-099 was a 66-year-old man with a relevant medical history of hypertension ("borderline hypertension") and tobacco use. The datasets and narrative conflict with regard to a prior medical history of CAD, with the datasets listing "coronary artery disease (occult)" beginning in the year prior to study enrollment and the narrative stating

"His past medical history was negative for diabetes, myocardial infarction, angina, angioplasty or coronary artery bypass surgery." The subject experienced an ST elevation myocardial infarction 64 days after his second injection of Heplisav-B. A cardiac catheterization demonstrated an acute 100% occlusion of the LAD with thrombus present. Balloon angioplasty was performed and two stents were placed. (PT = acute myocardial infarction). Triglycerides (205) and HgbA1c (8.7%) were elevated at the time of the event, though the subject had no known history of dyslipidemia or diabetes. Information for subject 140-099 was provided both in 125428.0.42 and 125428.0.67, in response to the 9 September 2016 IR. The event was adjudicated as an MI.

Reviewer comment: *While it may be assumed that the subject had some level of coronary artery disease prior to the study, based upon the 100% occlusion noted on-study, the reviewer cannot concur with a pre-existing diagnosis of occult CAD because the basis of this diagnosis in this case is unclear. The reviewer saw no evidence that the subject had a diagnosis of occult CAD at the time of study enrollment and this diagnosis appears to be retrospectively applied. The subject likely had diabetes pre-existing as the elevated HgbA1c was obtained within three months of study enrollment.*

The subject was discharged on warfarin, which was discontinued approximately three months later. He went on to report SAEs of acute systolic heart failure, pulmonary embolism, and left ventricular thrombus (LV) thrombus 284 days after dose 2 (discussed in Section 6.3.12.2). The CSR and submitted narrative for these SAEs suggest the AMI was complicated by an LV thrombus. However, additional information that the Applicant submitted indicate that the investigator believes the history of LV thrombus noted in one hospital note was an error.

Subject 126-206 was a 68-year-old man with a relevant medical history of CAD, prior MI with cardiac stent placement, hypertension, high cholesterol, sleep apnea on continuous positive airway pressure, deep vein thrombosis, Factor V Leiden mutation (unknown at study enrollment), and paroxysmal atrial fibrillation. He experienced an acute myocardial infarction with cardiogenic shock, requiring percutaneous intervention, intra-aortic balloon pump, and left ventricular assist device placement, 84 days after his second injection of Heplisav-B (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 122-174 was a 56-year-old man with a relevant medical history of hypertension, gout, hypercholesterolemia, septic shock, deep venous thrombosis, paroxysmal atrial fibrillation, morbid obesity, and prior tobacco use. He had multiple hospitalizations for urosepsis, atrial fibrillation, and latent tuberculosis (rule out active tuberculosis). The narrative states the subject lived in a shelter. He was admitted for unstable angina 95 days after his second injection of Heplisav-B, reporting intermittent chest pain for the previous three weeks. A perfusion scan showed a reversible/partially reversible defect, but a cardiac catheterization showed "no significant coronary artery disease." Troponin was undetectable. He had multiple subsequent hospitalizations, including for dyspnea and mycobacterium avium intracellular complex infection (PT = unstable angina). The event was not selected for adjudication based on PT.

Reviewer comment: *Based on the narrative, which states the cardiac catheterization did not show significant disease, this is not an AE of MI or unstable angina.*

Subject 139-037 was a 39-year-old woman with a relevant medical history of tobacco use, asthma, and hypertension. The subject experienced a non-ST elevation myocardial infarction 173 days after her second injection of Heplisav-B (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 103-189 was a 47-year-old man with a relevant medical history of hyperlipidemia, sleep apnea, hypertension, obesity, and low testosterone (taking testosterone). He experienced a non-ST elevation myocardial infarction 175 days after the second injection of Heplisav-B. Troponin-1 was elevated to 11.48 ng/mL and cardiac catheterization showed signs of a recent ruptured plaque in the proximal left anterior descending and medical management was recommended (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 101-154 was a 70-year-old woman with a relevant medical history of obesity and dyslipidemia who reported a non-ST elevation myocardial infarction 207 days after the dose 2 of Heplisav-B. She received a catheterization, which showed diffuse non-obstructive atherosclerotic coronary artery disease. There were wall motion abnormalities in the left ventricle, indicating the first diagonal branch was the most likely the culprit vessel per narrative. No percutaneous intervention was indicated, and she was treated medically (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 122-992 was a 53-year-old man with a relevant medical history of prior heroin addiction, hypertension, and prostate cancer, diagnosed one month prior to vaccination. He was discontinued from treatment at Week 4 when the site became aware of his prostate cancer. He experienced an ST-elevation myocardial infarction 294 days after the first injection of Heplisav-B. Cardiac catheterization showed 99% complex tubular lesion of the mid left anterior descending and a bare metal stent was placed (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 115-076 was a 69-year-old man with a relevant medical history of obesity, type 2 diabetes, hypertension, hyperlipidemia and prior tobacco use. He was taking phentermine beginning three years prior to study enrollment. The narrative reports the subject was seen by his PCP twice since study start for chest pressure, diagnosed as indigestion. These events are not reported as MAEs. He reported chest pain, was found have paroxysmal ventricular tachycardia and atrial fibrillation with rapid ventricular response. He was placed on anti-arrhythmics and multiple attempts at cardioversion were unsuccessful. He was then diagnosed with a non-ST elevation myocardial infarction 308 days after the second injection of Heplisav-B. Cardiac catheterization showed severe single-vessel coronary artery disease with thrombus, requiring thrombectomy and percutaneous intervention. Subsequently, he had a cardiac arrest post-catheterization and a cardiac defibrillator was implanted. He recovered and the events were considered resolved. (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 101-118 was a 63-year-old man with a relevant medical history of dyslipidemia, obesity, hypertension, coronary artery disease with two prior percutaneous interventions with stent placement, and Parkinson's disease. The narrative also notes a prior myocardial infarction. He experienced an ST elevation myocardial infarction 318 days after the second injection of Heplisav-B. A cardiac catheterization, which showed 100%

to the proximal circumflex, and a stent was placed (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 130-045 was a 64-year-old woman with a relevant medical history of type 2 diabetes, hypertension, obesity, peripheral vascular disease, sleep apnea, and chronic kidney disease. She experienced a non-ST elevation myocardial infarction 318 days after her second injection of Heplisav-B. A cardiac catheterization showed severe two-vessel CAD and three drug-eluting stents were placed (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 121-050 was a 61-year-old man with a relevant medical history of hypertension, low testosterone (on testosterone), and hypercholesterolemia who experienced an ST-elevation myocardial infarction 328 days after the second injection of Heplisav-B. A cardiac catheterization showed severe multi-vessel CAD and three stents were placed (PT = acute myocardial infarction). The event was adjudicated as an MI.

Engerix-B
Subject 112-291 was a 66-year-old man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes, obesity. He had a syncopal episode and was diagnosed with a non-ST elevation myocardial infarction 113 days after his third injection of Engerix-B. Cardiac catheterization showed multi-vessel CAD and he underwent a six-vessel coronary artery bypass graft (PT = acute myocardial infarction). The event was adjudicated as an MI.

Subject 138-102 was a 55-year-old man with a relevant medical history of angina due to possible arterial blockage, dyslipidemia, and former alcohol and cocaine dependency. As part of the evaluation for knee surgery the subject had a cardiac catheterization that showed multi-vessel disease. Nine days later and 202 days following the third dose of Engerix-B, the subject reported chest pain and underwent coronary artery bypass grafting (CABG). No EKG changes or troponin levels are reported (PT = coronary artery occlusion). The event was not selected for adjudication based on PT.

As per the Applicant's adjudications, fourteen subjects in the Heplisav-B group (0.25%) and 1 subject in the Engerix-B group (0.04%) experienced treatment-emergent AMIs in DV2-HBV-23 (RR = 6.97, 95% Koopman score CI 1.17, 41.44). None of the fatal events were adjudicated as MI. MI adjudications required evidence of myocardial necrosis by cardiac biomarkers and supporting clinical evidence (EKG changes, imaging).

Reviewer comment: *The clinical reviewer agrees with the adjudications that were performed. Two events were not selected for adjudication (in subject 106-312 in the Heplisav-B group and 138-102 in the Engerix-B group), but represent coronary ischemic events without evidence provided of an infarct, in the judgement of the clinical reviewer. Subject 122-174 with "unstable angina" and a cardiac catheterization demonstrating no abnormalities is the only subject described in this section who did not have an obvious acute coronary ischemic event. CBER statisticians endorse the Koopman score CI as the most accurate method to assess the CI for events of MI in study DV2-HBV-23.*

Cardiovascular risk factors in subjects who reported MIs: The table below is a reviewer-generated tabular summary of the timing and risk factors known at baseline for subjects reporting an SAE with a PT in the SMQ Narrow for MI. Events adjudicated as a MACE

are shaded, including one subject in each group with a fatal SAE adjudicated as a cardiovascular death, but not an MI. This table differs from the Applicant's table in 125428/0.42 integrated summary of safety, in that only events with evidence of presence of the specific risk factor at baseline are included here.

Table 34. CBER Analysis of timing of myocardial infarction (MI) following vaccination and baseline risk factors of subjects reporting MI, by treatment group, and ordered by increasing length of interval between most recent active dose and day of MI event, Safety Population, DV2-HBV-23

Treatment Group and Subject #	Preferred Term	Study Day of MI event	Day of MI event relative to most recent active dose	Most recent active dose #	Age/ Sex	Prior Known Ischemic Heart Disease	DM	HTN	DL	Current or former smoker*	Obesity
Heplisav-B											
141-110	AMI	28	3	2	61 F	**?**		**+**	**+**		
130-084	ACS†	8	8	1	50 M	**+**		**+**			
106-312	Coronary artery occlusion‡	14	14	1	64 F		**+**	**+**	**+**		
113-011	MI	81	53	2	68 F				**+**	**+**	
131-091	AMI†	85	58	2	69 M			**+**	**+**	**+**	
134-373	AMI	87	62	2	64 M			**+**	**+**	**+**	
112-090	AMI	93	64	2	53 M		**+**	**+**	**+**		**+**
140-099	AMI	87	64	2	65 M		**+¶**	**+**		**+**	
126-206	AMI	113	85	2	68 M	**+**		**+**	**+**		**+**
122-174	Angina Unstable‡§	123	96	2	56 M			**+**	**+**	**+**	**+**
139-037	AMI	202	174	2	39 F			**+**		**+**	
103-189	AMI	203	175	2	46 M			**+**	**+**		**+**
101-154	AMI	231	208	2	69 F				**+**		**+**
122-613	MI†	320	288	2	47 M		**+**				
122-992	AMI	295	295	1	52 M			**+**			
115-076	AMI	338	309	2	68 M		**+**	**+**	**+**	**+**	**+**
101-118	AMI	347	319	2	62 M	**+**		**+**	**+**		**+**
130-045	AMI	347	319	2	63 F		**+**	**+**			**+**
121-050	AMI	356	329	2	60 M			**+**	**+**		
Engerix-B											
135-070†	MI†	13	13	1	52 M	**+**				**+**	
112-291	AMI	272	115	3	65 M	**+**	**+**	**+**	**+**		**+**
138-102	Coronary artery occlusion‡	371	203	3	54 M	**+**			**+**		

Source: Reviewer-generated analysis from 125428/0.42, Module 5.3.5.1, datasets ADSL, ADAE, and ADMH and 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety.
Day 1 is day of administration. An event start day relative to the most recent active dose of x is x-1 days following the most recent dose.
Risk factors are marked if known at baseline as determined by datasets ADSL and ADMH, and by the narrative. Obesity is marked only if obese at study enrollment per datasets. Events shaded represent events that were adjudicated by the Applicant's analysis as events of cardiac death or MI

AMI: acute myocardial infarction, MI: myocardial infarction, CAD: coronary artery disease, DM: diabetes mellitus, HTN: hypertension, DL: dyslipidemia
+ Subject has risk factor
? Not clear (or incongruent information) from narrative and datasets if diagnosis of ischemic heart disease occurred prior to enrollment
* Current and former smoking presented as reported in the datasets and narratives; smoking in the study was defined as within the last year.
† Fatal event
‡ Event not selected for adjudication by PT.
§ Subject had a cardiac catheterization showing no coronary artery disease
¶ Subject did not have a baseline diagnosis of diabetes, but an elevated hemoglobin A1C within 3 months of first vaccination, suggesting pre-existing diabetes
\\ Subject did not have a known history of coronary artery disease, but had evidence of a remote infarct at autopsy. Date of death was study day 13.

All subjects who reported either a fatal or nonfatal SAE with a PT in the SMQ Narrow for MI also reported at least one risk factor for coronary artery disease, including history of coronary artery disease, hypertension, diabetes, hyperlipidemia, smoking, age, and medications that could increase the risk of cardiac events. Most subjects had multiple risk factors for cardiovascular disease; however, most did not have known coronary artery disease.

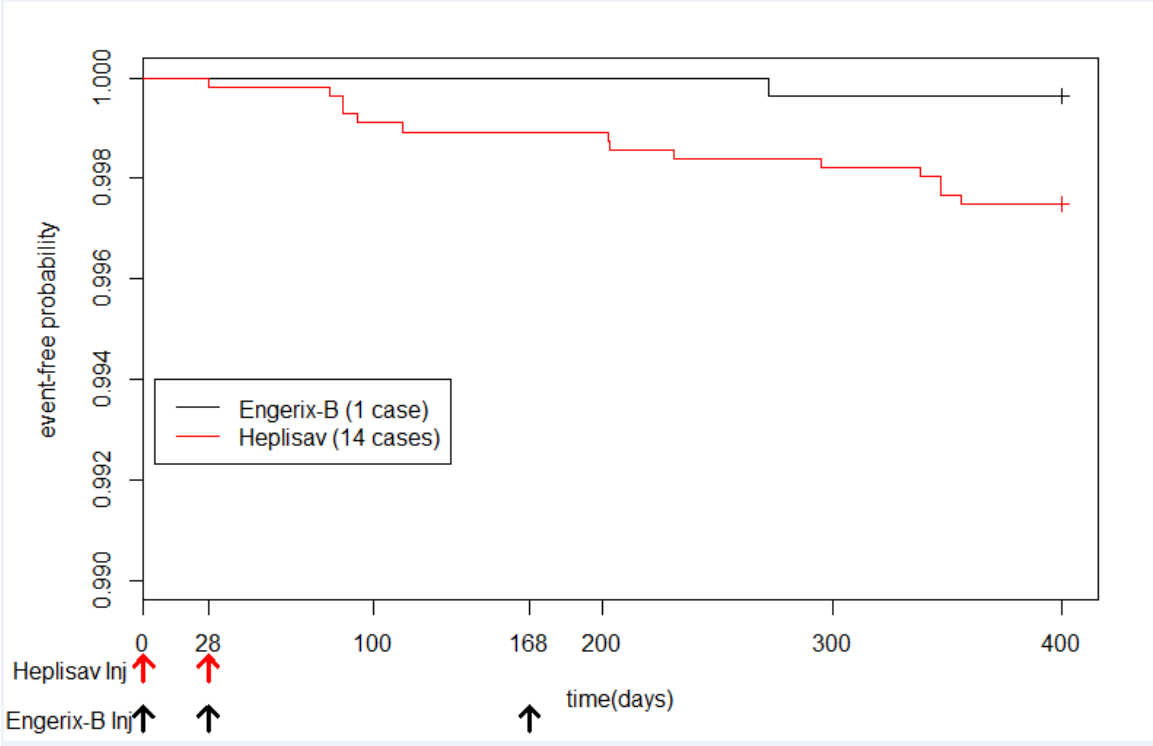
Reviewer comment: *Diabetics may be at an increased risk of acquiring HBV infection and ACIP recommends vaccination of diabetics 19 through 59 years of age. If you consider only events adjudicated as MI and the Applicant's pre-specified definition of diabetes (history of the disease and taking an antihyperglycemic agent), the risk of adjudicated MI in diabetics in the Heplisav-B and Engerix-B groups are equal (Two subjects in the Heplisav-B group, one subject in the Engerix-B group). However, if you include information from the narratives, two additional subjects in the Heplisav-B group that experienced adjudicated MIs, were also diabetic (subject 112-090 had diet-controlled diabetes, one had an elevated HgbA1c < three months after study enrollment), making the risk of MI in diabetics in the Heplisav-B group approximately twice that of diabetics in the Engerix-B group.*

Reviewer comment: *While subjects with SAEs of MI had significant risk of MI, cardiovascular risk factors were balanced at baseline between the treatment groups. Given the small number of events, particularly in subgroups, it is difficult to accurately estimate risk in these groups.*

Timing of MI SAEs: Within one month of the most recent active vaccination, three subjects in the Heplisav-B group and one subject in the Engerix-B group reported an SAE (fatal or non-fatal) of MI (by narrow SMQ). Within three months of the most recent active vaccination, nine subjects in the Heplisav-B group and one subject in the Engerix-B group reported an SAE of MI. Within 6 months of the most recent active vaccination, 12 subjects in the Heplisav-B group and 2 subjects in the Engerix-B group reported an SAE of MI. The remainder of MIs (seven subjects in the Heplisav-B group, one subject in the Engerix-B group) were reported greater than six months following the most recent active vaccination.

Figure 1 shows the Kaplan-Meier curve for events of MI in Study DV2-HBV-23 as determined by the Applicant's adjudication.

Figure 1. Kaplan-Meier curve for adjudicated myocardial infarction events from time of first injection in DV2-HBV-23



Source: CBER analysis 125428/0.42, Module 5.3.5.1, dataset ADAE and 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety.
Events of MI are included. Events of cardiovascular death not adjudicated as MI are not included.
Arrows show timing of injections.

Reviewer comment: *Risk of MI between the two treatment groups appears to diverge at approximately 3 months following the first vaccination, two months following the second vaccination, and persists throughout the study follow-up period. While the overall loss to follow-up in this study is low and similar between treatment groups, as discussed at the 28 July 2017 VRBPAC, it is unknown whether the early loss to follow-up would have contributed more subjects to the MI or death counts.*

When considering the number of events in a certain time period after vaccination, it is important to remember that the Engerix-B group will have greater observation time compared to the Heplisav-B group due to a three- vs. two-dose vaccine series. Therefore, when comparing events frequencies occurring within one month of last active injection, for example, Engerix-B subjects might be expected to have a 50% greater frequency of adverse events as they have 50% more observation time (three months vs.

two months). If comparing event frequencies greater than 6 months, Heplisav-B subjects would be expected to have more events because they have more observation time in this window (approximately 7 months/28 weeks vs. 8 weeks/2 months). All subjects were monitored for the same total length of time. For these reasons, the Kaplan-Meier plot above is the easiest way to conceptualize the differences in adverse events by treatment group.

Timing of event onset, particularly when far from vaccination, may be seen as decreasing the probability that an event may be related to vaccination. However, AE onset date may not always accurately capture the onset of disease progression (for example, subject 115-076's indigestion prior to the event of MI may have been angina). Additionally, the assumption that any event that occurs further from an inciting event than a particular time point is not related to that inciting event, does not account for mechanisms of biologic plausibility that either involve a prolonged effect of the inciting agent or that contribute to progression of disease that may lead to increased risk at a later time. SAEs of MI may be attributed to pre-existing coronary artery disease, either symptomatic or asymptomatic, prior to vaccination. However, pre-existing disease, either symptomatic or asymptomatic, does not rule out the possibility that vaccination may have contributed to accelerated disease resulting in an MI post-vaccination.

Other AEs not included as SAEs of MI: There was one additional subject (105-059), a 54-year-old woman who reported an SAE of AMI during the screening period prior to vaccination. This event is not included in discussion of MIs as this was not a treatment-emergent event. This subject was treated with balloon angioplasty, recovered, and received two doses of Heplisav-B beginning thirteen days after the event onset. The only other MAE she reported on-study was pharyngitis.

In 125428/0.63, in response to CR item 11, the Applicant provided additional information for subject 119-279, a 36-year-old woman with a six-month history of hypertension, hyperlipidemia, chest pain and myocardial ischemia. Six days after her second dose of Heplisav-B she reported an SAE of "atypical chest pain," which maps to a PT of chest pain in the General disorders SOC. The pain was responsive to nitroglycerin. The subject had no EKG changes, negative cardiac enzymes, essentially normal echocardiography, a small area of borderline to mild ischemia in the lateral wall on nuclear stress test, and negative electrocardiographic Persantine stress test. She was discharged and received follow-up with cardiology.

Reviewer comment: *There is no evidence of MI. However, this subject may have evidence of possibly treatment-emergent cardiac ischemia.*

There were additional subjects who reported non-serious MAEs with PTs that were either in the SMQ narrow for MI or that could indicate a cardiac ischemic event, who are not included in the above discussion and for whom CBER requested information in the 10 November 2016 CR.

- In 125428/0.74 and 125428/0.94, in response to CR item 26, the Applicant provided additional information on one Heplisav-B subject (128-042) who was diagnosed with an age-indeterminate MI by adenosine nuclear scan and EKG performed approximately 112 days following the first injection.

Reviewer comment: *EKGs were not assessed as part of study DV2-HBV-23. The exact timing of the silent MI is unknown. It is possible that this MI could have occurred following vaccination. This event highlights the limitations associated with post-hoc assessment of MI as opposed to prospective screening and assessment of all events.*

- Two events of troponin increased were reported in two subjects in the Engerix-B group in the setting of another SAE (urosepsis and diabetes mellitus inadequate control). In 125428.74, in response to CR item 27, the Applicant provided source documents indicating that the neither subject's clinical presentation was consistent with an AMI. Events were assessed by treating physicians as due the concurrent SAEs.

- In 125428/0.74, in response to CR item 4, the Applicant provided information on subject 122-631, a 60-year-old man who reported no medical history or medications at baseline, but was later reported to have chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, asthma, and anxiety and be on multiple medications. He received one dose of Engerix-B and was then lost to follow-up. As per the narrative, 13 months after the first injection, the site reported an MAE with verbatim term of "cocaine induced coronary artery vasospasm," and PT of Drug abuse, occurring approximately two months following the study vaccine, treated with one day of nitroglycerin. The narrative reports the subject was subsequently re-engaged. The subject reported an ER visit on the same date as the event of vasospasm, for COPD exacerbation (MAE). He reported a hospitalization of COPD two weeks later (SAE). The site was unable to obtain these medical records. The Applicant responded that the verbatim term "cocaine-induced coronary vasospasm" should have been captured as two MedDRA preferred terms of Drug abuse and Arteriospasm coronary.

  Reviewer comment: *Information is limited but does not indicate that this event was serious or that the subject had an MI. Recoding as two events does not change the overall balance of cardiac SAEs between the treatment groups or events of MI in the Engerix-B group.*

- In 125428/0.74, in response to CR item 4, the Applicant provided information on subject 125-359, a 53-year-old woman with a history of hypertension, depression, and osteoarthritis who reported non-serious MAEs of chest pain and cardiac catheterization. Following her second dose of Engerix-B, she complained of chest pain at a routine appointment, which she reported began three weeks following the first dose of Engerix-B. A stress test showed "a blockage in the anterior aspect of her heart" and a cardiac catheterization performed two months after her third vaccination with Engerix-B was reported by the subject to be "negative with no blockage."

  Reviewer comment: *The above MAEs do not appear to represent AMIs.*

CRFs and narratives for all subjects who reported an SAE in the Cardiac disorders SOC or an SAE of chest pain or non-cardiac chest pain were requested.

Reviewer comment: *Narratives were reviewed and no additional events clearly indicative of MI were identified. The reviewer identified subjects in both treatment arms with findings on EKG or other cardiac evaluations that may represent treatment-emergent cardiac ischemia or silent cardiac infarct. These events were not prospectively defined or monitored or evaluated post-hoc in a blinded, systematic fashion.*

Stroke: Events of stroke were evaluated by the CBER and as part of the Applicant's MACE analysis. As per the ADAE dataset, SAEs in the narrow SMQ for cerebrovascular disorders/central nervous system hemorrhages and cerebrovascular conditions, which includes ischemic, hemorrhagic and unknown strokes (events coded with PT of cerebrovascular accident), were reported in 20 subjects who received Heplisav-B (0.4%) and 6 subjects who received Engerix-B (0.2%). Narratives and CRFs of specific subjects who reported possible strokes were requested in the 9 September 2016 IR (item 11) and of all subjects who reported SAEs of stroke or transient ischemic attack were requested in the 10 November 2016 CR (item 28).

As part of the MACE analysis submitted in 125428/0.65, the Applicant conducted blinded adjudication of events of stroke, via the process described under Cardiac SAEs. The PTs selected by the Applicant's consultant identified 16 subjects with events that were reviewed for adjudication (11 subjects in the Heplisav-B group and five subjects in the Engerix-B group). PTs in the SMQ narrow for central nervous system hemorrhages and cerebrovascular conditions, but not selected for adjudication included transient ischemic attack (three Heplisav-B subjects, one Engerix-B subject), carotid artery stenosis (two Heplisav-B subjects), hypoxic ischemic encephalopathy (two Heplisav-B subjects), and subarachnoid hemorrhage (one Heplisav-B subject). The Applicant's consultants adjudicated 11 subjects in the Heplisav-B group (0.2%) and 4 subjects in the Engerix-B group (0.14%) as experiencing an event of stroke. Please see Section 8.4.2 for a description of the Applicant's analysis of stroke, MI, and CV death in the other two pivotal trials.

Reviewer comment: *Narratives were reviewed for agreement with adjudication. In the opinion of the reviewer, some events were missed by not including transient ischemic attack in the PTs selected for adjudication. Subject 131-109 was reported to have a TIA; however, per the narrative the subject had a "magnetic resonance imaging (MRI), which, revealed acute stroke in the right thalamus, with evidence of an old left thalamic stroke; this likely represented lacunar infarcts from hypertension." Please see the further discussion of this subject's diagnosis of Takayasu arteritis in Section 6.3.12.5. Subject 112-213 had a brain MRI showing a suspected acute on chronic infarct, but symptoms consistent resolving within hours. The event was reported as a TIA and was not reviewed by an adjudicator. Based upon other narratives and adjudications, it is possible an adjudicator may have considered this event a stroke. The reviewer agrees with the adjudications that were performed. The reviewer considers the subject 131-109 to have had a stroke. Therefore, the clinical reviewer considers the number of strokes in the Heplisav-B group to be 12 (0.2%) compared to 4 in the Engerix-B group (0.14%).*

As per information submitted by the Applicant in 125428/0.63, the timing of the stroke reported by one subject (131-103) was incorrect. Taking this into account, one Heplisav-B subjects (0.02%) and no Engerix-B subjects reported a stroke SAE within 30 days of last active injection and four Heplisav-B subjects (0.07%) and three Engerix-B subjects (0.1%) reported a stroke SAE within 90 days of last active injection.

Reviewer comment: *There is a numerical imbalance in the number of subjects who experienced strokes in DV2-HBV-23 with more subjects in the Heplisav-B group compared to the Engerix-B group. The small excess in events in the Heplisav-B group is observed after 3 months following the last active injection. Although the imbalance is small, it is more concerning coupled with the observations of MI in the study.*

Atrial fibrillation: An imbalance in MAEs, but not SAEs of atrial fibrillation was also observed with 16 subjects in the Heplisav-B group (0.29%) reporting 16 MAEs of atrial fibrillation and three subjects in the Engerix-B group (0.11%) reporting four MAEs of atrial fibrillation. In 125428/0.74, in response to item 29 of the 10 November 2016 CR letter, the Applicant submitted their analysis of the differences in MAEs of atrial fibrillation between treatment groups. Subjects in the group who reported atrial fibrillation were 50 to 70 years of age (median 65) and reported the event onset on day 8 to 327 after the last active injection. Subjects in the Engerix-B group were 59 to 67 years of age (median 65) and reported the event onset on day 47 to 189 days after the last active injection. Two subjects in the Heplisav-B group reported the onset within 30 days of the last active injection (both within two weeks) compared to none in the Engerix-B group. Atrial fibrillation was new in onset for 13 Heplisav-B recipients and 2 Engerix-B recipients.

The Applicant noted risk factors in all subjects that reported atrial fibrillation in both groups. They posit that there is no temporal association between atrial fibrillation and active treatment in either study group. No notable imbalances reported in studies DV2-HBV-10 and -16 (one subject in the Engerix-B group in study DV2-HBV-10 and four subjects in the Heplisav-B group in DV2-HBV-16, which had a 4:1 randomization ratio). The Applicant reports that there is no known association between TLR9 stimulation and atrial fibrillation. The Applicant also provided additional information regarding one subject (115-010) in the Heplisav-B group with atrial fibrillation onset 8 days after dose 1, noting that she had been wearing a heart monitor for heart palpitations for three weeks prior to her first dose.

Reviewer comment: *There are numerous factors that can lead to atrial fibrillation. In theory, a common mechanism could be contributing to both the events of MI and atrial fibrillation. There were four subjects who reported both MI (by PT in the SMQ narrow for MI) and atrial fibrillation (three Heplisav-B recipients, one Engerix-B recipient). Two Heplisav-B subjects reported MI at least one month prior to the event of atrial fibrillation and one Heplisav-B reported events concurrently. Otherwise, subjects with atrial fibrillation did not also report events of coronary ischemia. In the judgement of the clinical reviewer, it is not clear if imbalances in atrial fibrillation and MI are related, but it is noted that the atrial fibrillation imbalance occurs only when analyzing MAEs and not when SAEs are analyzed.*

Additional SAEs of interest: In the 9 September 2016, the CBER also requested additional information for specific subjects with SAEs. Responses are summarized here:

- Subject 125-113 who reported an SAE of lung cancer, reported to be a moderately differentiate adenocarcinoma.

Safety in selected subgroups - diabetics: A reviewer-generated analysis was conducted to evaluate safety in diabetic subjects given that the Applicant pre-specified an immunogenicity assessment in this subgroup as a primary endpoint and included immunogenicity data from this subgroup in the package insert (Table 35). In

125428/0.105 the Applicant, in response to information requested during labeling discussions, the Applicant submitted their analysis of these results. The Applicant's analysis, discussed below, is presented differently than the reviewer's analysis, but the numbers do not conflict.

Table 35. Reviewer-generated summary of subjects with protocol-defined type 2 diabetes with selected treatment-emergent safety outcomes by treatment group, Safety Population, Study DV2-HBV-23

Safety outcome	Heplisav-B N = 762 n (%)	Engerix-B N = 381 n (%)	Expected % of subjects with SAEs in Heplisav-B group†
MAEs	462 (60.6)	217 (57.0)	-
SAEs	90 (11.8)	26 (6.8)	-
- within 30 days of active vaccination	12 (1.6)	7 (1.8)	1.2
- within 90 days of active vaccination	32 (4.2)	19 (5.0)	2.9
- within 180 days of active vaccination	56 (7.4)	26 (6.8)	4.0
MACE*	6 (0.8)	2 (0.5)	-
MI**	2 (0.3)	1 (0.3)	-
Death	5 (0.7)	1 (0.3)	-

Source: CBER analysis 125428/0.42, Module 5.3.5.1, dataset ADAE and ADSL and 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety.
N = number of subjects in each treatment group
n = number of subjects reporting event
* MACE = Major adverse cardiovascular events as adjudicated by the Applicant
** MI = Myocardial infarction as adjudicated by the Applicant
† based on Engerix-B % and number of months in the observation period

Treatment emergent MAEs (including SAEs) were similar between treatment groups when stratified by diabetic status, though diabetics reported more MAEs than non-diabetics (not shown). Treatment-emergent SAEs were similar between treatment groups in non-diabetics, but were higher in the Heplisav-B group compared to the Engerix-B group in diabetics.

Per the reviewer's analysis, rates of SAEs within a specified time period following any active vaccination appear similar between the two treatment groups up to 180 days. However, when one accounts for the greater period of observation time for the Engerix-B group in these analyses, due to a three versus two dose regimen, there is a higher rate of subjects reporting SAEs in the Heplisav-B group compared to the Engerix-B group at 30 days, 90 days, and 180 days. The Applicant notes that 12 diabetic subjects in the Heplisav-B group (1.6%) and 3 diabetic subjects in the Engerix-B group (0.8%) reported SAEs within 28 days of the first two active injections. The Applicant also reports that the rate of SAE reporting was lower in the Engerix-B group in the latter third of the study time period (2.3%) compared to the rates in the Engerix-B group in the first two thirds of the study (7.7 – 10.1%) and compared to the Heplisav-B group during each third of the study (10.6 – 12.2%).

As per the reviewer's analysis, the imbalance in SAEs was observed in several SOCs. In the following SOCs, rates of SAEs in diabetic subjects were observed to be at least 0.5% in one treatment group and at least twice as high in one group compared to the

other: neoplasms (Heplisav-B 1.3%, Engerix-B 0.3%), cardiac disorders (Heplisav-B 2.9%, Engerix-B 1.1%), injury, poisoning, and procedural complications (Heplisav-B 0.9%, Engerix-B 0.3%), psychiatric disorders (Heplisav-B 0.7%, Engerix-B 0), metabolism and nutrition (Heplisav-B 0.7%, Engerix-B 0.3%), and skin and subcutaneous tissue disorders (Heplisav-B 0.26%, Engerix-B 0.52%,). The Applicant identifies three preferred terms that are reported by five subjects in the Heplisav-B group (0.7%) – cardiac failure congestive and pneumonia, each reported by one subject in the Engerix-B group (0.3%), and coronary artery disease, reported by two subjects in the Engerix-B group (0.5%). As per the Applicant, four of five Heplisav-B subjects with congestive heart failure had exacerbations of heart failure, and causes of pneumonia were varied (for example, hospital-acquired in two subjects and complication of influenza infection, urosepsis, and community-acquired in one subject each). The reviewer notes additional subjects who reported events of likely coronary ischemia, such that 10 subjects in the Heplisav-B group and 2 subjects in the Engerix-B group reported SAEs with a PT with a higher level group term of coronary artery disorders, including (acute) myocardial infarction and angina pectoris.

There were more deaths in diabetic subjects in the Heplisav-B group compared to the Engerix-B group. Deaths in the Heplisav-B group were due to cirrhosis (107-176), myocardial infarction (122-613), hypertensive heart disease (112-311), cardiac arrest (133-120), and acute respiratory distress syndrome (121-090). The subject in the Engerix-B group died of cardiopulmonary arrest (130-392). Based on MACE adjudications, the four diabetic subjects in the Heplisav-B group who died due to a PT in the cardiac disorders SOC, were adjudicated as having an unknown cause of death. The subject in the Engerix-B group was adjudicated as having a non-cardiovascular death, but also as having a stroke earlier on-study.

Reviewer comment: *A greater proportion of diabetic subjects reported SAEs in the Heplisav-B group compared to the Engerix-B group. The excess SAEs appear to be distributed throughout the entire study follow-up period. Please also see the discussion above regarding MIs in two additional diabetic subjects who did not meet the protocol definition of diabetes. Subjects were randomized based upon diabetic status. Hemoglobin A1C levels in all subjects were similar between treatment groups at baseline, but slightly greater in Heplisav-B subjects at Week 28. The differences in SAE rates in diabetic subjects between treatment groups appears to be distributed through several different SOC's; therefore, attributing causation to the vaccine for any particular SAE or the diabetic subgroup as a whole is difficult. However, while adjudicated SAEs of MI occurred at the same frequency in diabetics in both treatment groups, it is noted that an imbalance in coronary artery disease, which did not necessarily result in evidence of infarction, was reported in diabetic subjects with greater frequency in the Heplisav-B group.*

Safety in selected subgroups – by age: A reviewer-generated analysis was conducted to evaluate safety in subjects by the prespecified age subgroups. The Applicant proposed inclusion of immunogenicity results in the package insert by these same subgroups. (Table 36).

Table 36. Reviewer-generated analysis of subjects reporting serious adverse events by age group and by treatment group, Safety Population, Study DV2-HBV-23

Age group (years)	Heplisav-B N	Heplisav-B n (%)	Engerix-B N	Engerix-B n (%)
18 – 29	260	5 (1.9)	131	6 (4.6)
30 – 39	872	26 (3.0)	430	14 (3.3)
40 – 49	1269	68 (5.4)	632	28 (4.4)
50 – 59	1765	108 (6.1)	895	50 (5.6)
≥ 60	1421	138 (9.7)	693	50 (7.2)

Source: CBER analysis 125428/0.42, Module 5.3.5.1, dataset ADAE and ADSL.
N = number of subjects in each treatment and age group
n = number of subjects reporting event

Reviewer comment: *The percentage of subjects reporting SAEs is slightly higher in the Heplisav-B group for ages 40 – 49 and older than 60 years of age. However, it is difficult to draw conclusions in this analysis regarding relationship to vaccination for these subgroups because subjects were randomized by less than 40 years of age and 40 years of age and older, not based upon these smaller age groups. There may be additional confounding factors contributing to the differences between treatment groups in these subgroups that are not accounted for in this analysis.*

Concomitant Medications

All concomitant medications were entered into the CRFs from 28 days prior to vaccination through Week 28 and select concomitant medications (immunosuppressive medications; immunoglobulins; blood products; vaccines; any medications, including over-the-counter medications, administered for treatment of a MAE, AESI, AIAE, or SAE; and any prohibited medication pre-specified in the protocol) were collected from Week 28 through Week 56. As discussed in Section 6.3.10.1.2, no clinically significant differences were noted in baseline medication use. The Applicant did not provide a specific analysis of concomitant medication use after vaccination. The below analyses are reviewer-generated.

A similar proportion of subjects in each treatment group reported concomitant medication use or change through both Week 28 (49.3% Heplisav-B, 49.4% Engerix-B) and through Week 56 (56.8% Heplisav-B, 57.0% Engerix-B). The subjects in each treatment group reported a similar average number of new or changed concomitant medications (3.2 Heplisav-B and 3.3 Engerix-B through Week 28; 4.4 Heplisav-B and 4.4 Engerix-B through week 56). The table below shows the number and proportion of subjects reporting new or changed concomitant medication of select medication classes.

Table 37. CBER-generated analysis of number and proportion of subjects reporting new or changed concomitant medications in medication classes potentially used to treat cardiac conditions or adverse events of special interest, Safety Population, Study DV2-HBV-23

Medication Class	Through Week 28 Heplisav-B N = 5587 n (%)	Through Week 28 Engerix-B N = 2781 n (%)	Through Week 56 Heplisav-B N = 5587 n (%)	Through Week 56 Engerix-B N = 2781 n (%)
Agents acting on the renin-angiotensin system	170 (3.0%)	88 (3.2%)	240 (4.3%)	113 (4.1%)
Analgesics	645 (11.5%)	341 (12.3%)	907 (16.2%)	492 (17.7%)

Medication Class	Through Week 28 Heplisav-B N = 5587 n (%)	Through Week 28 Engerix-B N = 2781 n (%)	Through Week 56 Heplisav-B N = 5587 n (%)	Through Week 56 Engerix-B N = 2781 n (%)
Antibiotics and chemotherapeutics for dermatological use	42 (0.8%)	12 (0.4%)	68 (1.2%)	21 (0.8%)
Antihypertensives	23 (0.4%)	13 (0.5%)	34 (0.6%)	16 (0.6%)
Anti-inflammatory and antirheumatic products	409 (7.3%)	202 (7.3%)	570 (10.2%)	290 (10.4%)
Antipsoriatics	1 (0.02%)	0	1 (0.02%)	0
Antithrombotic agents	113 (2.0%)	42 (1.5%)	194 (3.5%)	76 (2.7%)
Beta blocking agents	90 (1.6%)	36 (1.3%)	142 (2.5%)	55 (2.0%)
Calcium channel blockers	63 (1.1%)	31 (1.1%)	101 (1.8%)	45 (1.6%)
Cardiac therapy	28 (0.5%)	18 (0.7%)	53 (1.0%)	25 (0.9%)
Corticosteroids for systemic use	302 (5.4%)	156 (5.6%)	463 (8.3%)	243 (8.7%)
Corticosteroids, dermatological preparations	55 (1.0%)	44 (1.6%)	88 (1.6%)	62 (2.2%)
Diuretics	76 (1.4%)	39 (1.4%)	109 (2.0%)	51 (1.8%)
Drugs used in diabetes	180 (3.2%)	93 (3.3%)	266 (4.8%)	133 (4.8%)
Immune sera and immunoglobulins	1 (0.02%)	0	2 (0.04%)	1 (0.04%)
Immunosuppressants	2 (0.04%)	0	2 (0.04%)	0
Lipid modifying agents	160 (2.9%)	77 (2.8%)	225 (4.0%)	108 (3.9%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Module 5.3.5.1, dataset ADCM of study DV2-HBV-23

There were no notable differences between study groups in select medication classes potentially used to treat cardiac conditions or AESIs through Week 28 or Week 56. Antibiotics for dermatologic use were reported more frequently in Heplisav-B recipients. It is possible that certain dermatologic AESIs may be treated as infections initially. However, corticosteroids for dermatologic use were reported more frequently in Engerix-B recipients. Antithrombotic agents, which include aspirin used for cardio-protection, and beta-blocking agents are reported at slightly higher rates in subjects who received Heplisav-B compared to subjects who received Engerix-B. Aspirin use in this class was reported by 1.8% of Heplisav-B subjects and 1.4% of Engerix-B subjects.

Two subjects were recorded as having new use of immunosuppressant medication within 28 weeks of first vaccination in the Heplisav-B group. Subject 137-059 had an undisclosed long-standing history of rheumatoid arthritis and polymyalgia rheumatica at enrollment and began infliximab approximately two weeks following his second dose. It is not clear that this was an exacerbation of disease. Per the narrative, subject 102-089 had an undisclosed history of psoriasis and was being treated with etanercept at study enrollment, despite it being recorded as a new medication.

Reviewer comment: *This analysis did not identify any safety concerns regarding medications, such as anti-inflammatories, that could potentially be used to treat AESIs prior to diagnosis. There are small imbalances in antithrombotic agents, including*

aspirin, and beta-blockers, which, in the context of the cardiac events observed in this study, may be supportive evidence of an imbalance in cardiac events.

6.3.12.5 Adverse Events of Special Interest (AESI)

Sixty-one subjects reported at least one potential new-onset AESI that was referred to the SEAC for evaluation. As clarified by the Applicant in 125428/0.74, in response to CR item 32, 39 subjects who received Heplisav-B (0.70%) reported 41 AEs evaluated by investigators as a potential AESIs and 22 subjects who received Engerix-B (0.79%) reported 27 AEs, representing 24 diagnoses, that were evaluated by investigators as a potential AESI. Two subjects who received Engerix-B reported multiple AEs that occurred concurrently and were assessed together as one group of symptoms or diagnosis. Please see Appendix A for the pre-specified non-comprehensive list of AESIs in DV2-HBV-23. Tables 38 and 39 present the list of treatment-emergent events that investigators referred to the SEAC for adjudication.

Table 38. Adverse events of special interest referred to the Safety Evaluation and Adjudication Committee for review in the Heplisav-B Group, Safety Population, Study DV2-HBV-23

Body system	Subject #	Age Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per Investigator	AI per SEAC	New Onset per SEAC	Related per SEAC	New Onset AESI per Reviewer	Background Incidence per year[§]
Endocrine	130-115	49 F	Autoimmune thyroiditis	1	0	-	Not recovered	Possibly	Y	N	N	N	-
	125-133	45 F	Autoimmune thyroiditis	2	14	-	Not recovered	Possibly	Y	N	N	N	-
	108-070	51 F	Hypothyroidism	2	45	-	Not recovered	No	Y	N	N	N	-
	123-086	59 F	Hypothyroidism	2	139	103	Recovered	No	N	-	-	N	-
	110-030	51 F	Hypothyroidism (autoimmune)	2	160	60	Recovered	No	Y	N	N	N	-
	103-108	59 F	Hypothyroidism	2	213	-	Not recovered	No	N	-	-	N	-
	138-141	43 F	Hypothyroidism	2	233	-	Not recovered	No	N	-	-	Y	-
	136-149	60 F	Hypothyroidism*‡	2	245	-	Recovering	No	Y	Y	N	Y	350 per 100,000 women[38¶]
	112-326	51 M	Hypothyroidism	2	337	-	Not recovered	Possibly	N	-	-	N	-
	114-027	54 M	Basedow's Disease	2	43	-	Not recovered	No	Y	N	N	Y	-
	118-056	46 F	Basedow's Disease	2	64	17	Recovered	No	Y	N	N	N	-
	107-140	59 M	Hyperthyroidism	1	3	-	Not recovered	No	Y	N	N	N	-
	128-042	64 M	Hyperthyroidism	1	15	413	Recovered	No	N	-	-	N	-
	133-107	43 M	Thyroid function normal	2	165	1	Recovered	No	N	-	-	N	-
GI/Liver	114-022	67 M	Colitis ulcerative	2	219	-	Not recovered	No	Y	N	N	N	-
	136-200	46 F	Colitis ulcerative*	2	220	-	Not recovered	No	Y	Y	N	Y	2.2-14.3 per 100,000[39]
	125-442	44 M	Colitis ulcerative	2	232	91	Recovered	No	Y	N	N	N	-
	122-076	32 M	Colitis	2	91	-	Not recovered	No	Y	N	N	Y	-

Body system	Subject #	Age Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per Investigator	AI per SEAC	New Onset per SEAC	Related per SEAC	New Onset AESI per Reviewer	Background Incidence per year[§]
	139-035	63 F	Colitis	2	307	-	Unknown	No	N	-	-	N	-
	109-055	53 F	Biliary cirrhosis primary	2	248	-	Not recovered	No	Y	N	N	N	-
Metabolic	104-070	60 M	Type 1 diabetes mellitus	2	189	-	Not recovered	No	Y	N	N	N	-
Musculoskeletal	134-228	68 M	Myalgia	0	-2402	-	Not recovered	No	N	-	-	N	-
	129-084	62 F	Systemic lupus erythematosus	2	41	-	Not recovered	Possibly	Y	N	N	Y	-
	132-154	54 F	Sjogren's Syndrome (and Raynaud)	2	207	-	Not recovered	No	N	-	-	N	-
	102-163	45 F	Rheumatoid arthritis	2	279	-	Not recovered	No	N	-	-	N	-
	126-038	68 M	Polymyalgia rheumatica*	2	291	-	Not recovered	Possibly	Y	Y	N	Y	52.5 per 100,000 (≥ 50 years old) [40, 41, 42]
Neurologic/Eye	105-198	66 M	Diabetic lumbosacral plexopathy (initially CIDP)	0	-30	-	Not recovered	No	N	-	-	N	-
	134-044	49 M	VIIth nerve paralysis	1	9	77	Recovered	Possibly	N	-	-	Y	13-34 per 100,000[43]
	102-146	49 F	VIIth nerve paralysis	2	0 (55 after Dose 1)	29	Recovered	No	N	-	-	Y	13-34 per 100,000[43]
	116-323	31 F	VIIth nerve paralysis	2	169	38	Recovered	No	N	-	-	Y	13-34 per 100,000[43]

Body system	Subject #	Age Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per Investigator	AI per SEAC	New Onset per SEAC	Related per SEAC	New Onset AESI per Reviewer	Background Incidence per year[§]
	117-119	49 M	VIIth nerve paralysis (and diplopia)	2	171	-	Not recovered	No	N	-	-	Y	13-34 per 100,000[43]
	131-028	52 M	VIIth nerve paralysis	2	255	-	Recovering	No	N	-	-	Y	13-34 per 100,000[43]
	106-271	43 M	VIth nerve paralysis	2	120	35	Recovered	No	N	-	-	Y	-
	134-064	49 M	VIth nerve paralysis†	2	158	69	Recovered	Possibly	N	-	-	Y†	-
	117-119	49 M	Diplopia† (and VIIth nerve paralysis)	2	101	112	Recovered	No	N	-	-	Y†	-
	111-056	61 F	White matter lesion	2	145	-	Not recovered	No	N	-	-	N	-
Skin	133-026	43 M	Dermatitis psoriasiform (initially psoriasis)	2	18	-	Not recovered	Possibly	N	-	-	N	-
	131-035	43 F	Interstitial granulomatous dermatitis	2	70	-	Recovering	Possibly	N	-	-	Y	Unknown
	108-013	52 F	Alopecia areata*	2	228	-	Recovering	Possibly	Y	Y	N	Y	8.8-29.3 per 100,000[43]
Vascular	131-109	49 M	Takayasu arteritis	2	61	-	Not recovered	No	N	-	-	N	-
	132-154	54 F	Raynaud phenomenon (and Sjogren's)	2	207	-	Not recovered	No	N	-	-	Y	-

Source: Adapted from BLA STN 125428/0.42, Module 5.3.5.1, Adverse Event Listings, Listing 16.12.6.1, pp. 2308 – 2314.
AI = autoimmune
SEAC = Safety Evaluation and Adjudication Committee
AESI = adverse event of special interest
* SEAC assessed new-onset autoimmune event
† Alternative plausible cause of diabetes by SEAC and reviewer assessment; events are not considered immune-mediated
‡ Alternative plausible cause of hypothyroidism (Hashimoto's thyroiditis) is papillary thyroid carcinoma by SEAC and reviewer assessment; event is still considered immune-mediated

§ Background incidences provided for new-onset SEAC adjudicated autoimmune events, SEAC-confirmed diagnoses of new-onset AESIs (immune-mediated), and the event of granulomatous dermatitis for which systemic disease was not ruled out.
¶ Incidence of spontaneous overt hypothyroidism due to any cause

Table 39. Adverse events of special interest referred to the Safety Evaluation and Adjudication Committee for evaluation in the Engerix-B Group, Safety Population, Study DV2-HBV-23

Body system	Subject #	Age Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per Investigator	AI per SEAC	New Onset per SEAC	Related per SEAC	New Onset AI per Reviewer	Background Incidence per year
Endocrine	128-156	62 F	Autoimmune thyroiditis	2	45	-	Not recovered	No	Y	N	N	N	-
	139-090	57 M	Autoimmune thyroiditis	3	14	-	Not recovered	Possibly	Y	N	N	N	-
	112-170	70 F	Hypothyroidism (and Celiac)	3	76	-	Not recovered	Possibly	N	-	-	Y	-
	126-098	57 F	Hypothyroidism	3	129	-	Not recovered	Possibly	N	-	-	Y	-
	134-305	50 F	Hypothyroidism	3	137	-	Not recovered	No	Y	N	N	N	-
	114-044	65 F	Hypothyroidism	3	139	-	Not recovered	Possibly	N	-	-	N	-
	118-111	39 F	Hypothyroidism	3	161	-	Not recovered	No	Y	N	N	N	-
	141-052	36 M	Basedow's disease	2	42	98	Recovered	No	Y	N	N	N	-
	128-175	60 F	Basedow's disease (and cerebral ischemia)	3	144	-	Recovered	Possibly	Y	N	N	N	-
	139-254	60 M	Blood thyroid stimulating hormone increased	2	19	268	Recovered	No	N	-	-	N	-
GI	112-170	70 F	Celiac disease (and hypothyroidism)	1	14	-	Not recovered	No	Y	N	N	N	-
	133-214	70 M	Celiac disease	3	96	-	Not recovered	Possibly	Y	N	N	N	-
	115-124	67 F	Dry mouth (initially reported as Sjogren's)	2	237	-	Not recovered	No	N	-	-	N	-

Body system	Subject #	Age Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per Investigator	AI per SEAC	New Onset per SEAC	Related per SEAC	New Onset AI per Reviewer	Background Incidence per year
Musculoskeletal	112-015	37 F	Arthralgia (and migraine and rash)	1	19	-	Not recovered	Possibly	N	-	-	N	-
	125-181	47 M	Arthralgia (and myalgia)	1	20	-	Not recovered	Possibly	N	-	-	N	-
	125-181	47 M	Myalgia (and arthralgia)	1	20	-	Not recovered	Possibly	N	-	-	N	-
	116-118	35 F	Mixed connective tissue disease	2	69	-	Not recovered	No	Y	N	N	N	-
Neurologic/Eye	112-015	37 F	Migraine	1	2	168	Recovered	Possibly	N	-	-	N	-
	129-112	69 F	Demyelinating polyneuropathy	2	39	-	Recovering	No	N	-	-	N	-
	134-123	29 M	VIIth nerve paralysis	3	26	178	Recovered	Possibly	N	-	-	Y	13-34 per 100,000[43]
	128-175	60 F	Cerebral ischemia (and Basedow's disease)	3	186	-	Not recovered	No	N	-	-	N	-
	111-014	39 F	Retinal exudates	3	92	40	Recovered	No	N	-	-	N	-
Skin	128-207	64 F	Cutaneous lupus erythematous	3	196	-	Not recovered	Possibly	Y	N	N	N	-
	112-015	37 F	Rash	2	23	58	Recovered	Possibly	N	-	-	N	-
	122-091	63 F	Lichen planus	3	29	-	Not recovered	No	Y	N	N	N	-
	101-181	63 M	Lichen planus	3	117	-	Not recovered	No	Y	N	N	Y	-
	103-119	66 M	Lichenoid keratosis	3	50	117	Recovered	Possibly	N	-	-	Y	-

Source: Adapted from BLA STN 125428/0.42, Module 5.3.5.1, Adverse Event Listings, Listing 16.12.6.1, pp. 2308 – 2314.
AI = autoimmune
SEAC = Safety Evaluation and Adjudication Committee
AESI = adverse event of special interest
§ Background incidences provided for SEAC-confirmed diagnoses which were new-onset AESIs (immune-mediated).

The following is a summary of SEAC adjudications:

- No events were related to study vaccination.
- Four events in four subjects in the Heplisav-B group were new-onset autoimmune events – alopecia areata (subject 108-013), ulcerative colitis (136-200), polymyalgia rheumatica (126-038), and hypothyroidism (136-149). No events in the Engerix-B group were new-onset autoimmune events.
    - Hypothyroidism was diagnosed as Hashimoto's thyroiditis, assessed by the SEAC as due to a subsequently diagnosed papillary thyroid carcinoma.
- Five events of VIIth nerve paralysis (Bell's palsy) in the Heplisav-B group and one in the Engerix-B group were not assessed as autoimmune events by the SEAC, but were new in onset and are counted as immune-mediated by the Applicant.
- One event of VIth nerve paralysis (134-064) in the Heplisav-B group was adjudicated by the SEAC (and specialist) as secondary to diabetes and not autoimmune.
- One event of diplopia (117-119) in the Heplisav-B group was diagnosed as IIIrd nerve palsy and adjudicated by the SEAC and specialist as secondary to diabetes and not autoimmune. (Subject was later diagnosed with Bell's palsy.)
- Five additional events in four subjects who received Heplisav-B were new-onset events with a preferred term on the AESI list. The diagnosis was not confirmed by the SEAC for these events, and thus, the SEAC did not consider the events autoimmune – rheumatoid arthritis (102-163), Takayasu arteritis (131-109), VIth nerve paralysis (subject 106-271), and Sjogren's syndrome and Raynaud phenomenon in the same subject (132-154).
- One subject diagnosed with granulomatous dermatitis (131-035) was assessed as not having an autoimmune event.

As a result, the Applicant lists 14 subjects reporting AESIs (by preferred term) in the Heplisav-B group (0.3%) (Bell's palsy, n = 5; alopecia areata; hypothyroidism; polymyalgia rheumatica; ulcerative colitis; rheumatoid arthritis; Takayasu arteritis, VIth nerve paralysis in two subjects; and Sjogren's syndrome and Raynaud phenomenon in one subject), and one subject in the Engerix-B group (0.04%) (Bell's palsy). This assessment includes the additional events with unconfirmed diagnoses per the SEAC. The SEAC determined that there were four new-onset autoimmune events in four subjects (alopecia areata, hypothyroidism, polymyalgia rheumatica, and ulcerative colitis), none of them related to vaccination and one of them related to another cause (hypothyroidism). The Applicant considers the events of Bell's palsy new-onset immune-mediated conditions. In summary, the Applicant identifies nine new-onset immune-mediated conditions in the Heplisav-B group (Bell's palsy in five subjects, alopecia areata, hypothyroidism, polymyalgia rheumatica, and ulcerative colitis) and one new-onset immune-mediated condition in the Engerix-B group (Bell's palsy).

Reviewer comment: *A similar proportion of subjects in each treatment group reported events that were referred to the SEAC for review. The SEAC Charter did not specify a definition of autoimmune disease and the SEAC did not consider all AESIs autoimmune. In the opinion of the clinical reviewer, the SEAC used relatively strict criteria to determine an event was a new-onset diagnosis of autoimmune disease. However, their blinded assessment determined that there was a small number of new-onset autoimmune events reported exclusively in the Heplisav-B group (four subjects). There is a numerical*

imbalance between treatment groups in events the Applicant identifies as new-onset immune-mediated events with 9 subjects in the Heplisav-B group (0.16%) and 1 subject in the Engerix-B (0.04%) group reporting such events.

In their summary of AESIs, on page 88 of the DV2-HBV-23 CSR (125428/0.42), it is not clear why the Applicant does not include the AE of diplopia, which was determined by the specialist and the SEAC to be due to a third cranial nerve palsy, secondary to diabetes. However, this event was reported in a subject who also reported Bell's palsy and does not change their final count of nine subjects in the Heplisav-B group and one subject in the Engerix-B group.

While there is an imbalance between treatment groups, numbers are small and the immune-mediated events diagnosed and confirmed by the SEAC in this study are relatively common immune-mediated events. However, with the exception of one event of Bell's palsy in a subject who received Engerix-B, an event which has been reported following Engerix-B vaccination[24], immune-mediated events were reported exclusively in the Heplisav-B group. In the 9 September 2016 IR (item 5), CBER asked the Applicant for any additional analyses they conducted to evaluate this imbalance; the Applicant responded in 125428/0.67 that they had not performed additional analyses. CBER had no additional questions for the Applicant.

The reporting of new-onset AESIs, including autoimmune events, is difficult to capture even in the setting of a controlled clinical trial for the following reasons:

- Onset may be insidious or evolve over time, symptoms are often non-specific, and diagnosis may not be immediate, or even within the study period.
- Subjects may have pre-existing conditions that complicate the diagnosis (for example, osteoarthritis), particularly in the population in which DV2-HBV-23 was conducted
- Variations among experts regarding diagnostic criteria

Reviewer comment: *The clinical reviewer reviewed the narratives, including SEAC adjudication, for all the events referred to the SEAC. In the opinion of the clinical reviewer, the SEAC tended to adjudicate events as not autoimmune unless definitive evidence was provided to establish autoimmunity. For the reasons stated above, in many cases a diagnosis was not clearly established, onset of symptoms was in question, or there was disagreement between treating physician, specialist, and/or the SEAC. The SEAC's method reduced or eliminated false positive AESIs. As false negatives may be more concerning for safety assessments, the clinical reviewer identified potential AESIs reviewed by SEAC for which the question of an immune-mediated process was not sufficiently ruled out. In this analysis, if a physician or specialist diagnosed a subject with an AESI and clear evidence was not presented to determine that diagnosis was most likely pre-existing or incorrect, the event was assessed as a new-onset AESI.*

The following is a summary of this analysis by the reviewer:

- The reviewer agreed with the SEAC that four events in four subjects in the Heplisav-B group were new-onset autoimmune events – alopecia areata (subject 108-013), ulcerative colitis (136-200), polymyalgia rheumatica (126-038), and hypothyroidism/Hashimoto's thyroiditis (136-149). The reviewer agreed with the

SEAC that the event of hypothyroidism was possibly related to papillary thyroid carcinoma.

- Five AESIs of Bell's palsy were reported in the Heplisav-B group and one in the Engerix-B group. CBER considers Bell's palsy potentially immune-mediated.
- The reviewer agreed with the SEAC's assessment that one subject with VIth nerve palsy (134-064) and one subject with diplopia (diagnosed as IIIrd nerve palsy) (117-119), both in the Heplisav-B group, had AESIs in which there was a reasonable possibility the events were due to diabetes.
- Of the five additional new-onset events in four subjects who received Heplisav-B, in which a diagnosis was not confirmed by the SEAC,
    - The reviewer agrees with the specialist and SEAC, that a clear diagnosis of rheumatoid arthritis (102-163) was not made. This may represent an evolving AESI as new-onset laboratory abnormalities were noted.
    - Takayasu arteritis (131-109) was confirmed by two CBER consultants. However, the consultants determined that the diagnosis was not new-onset (see details below).
    - The reviewer agrees with the SEAC that there was no clear diagnosis of VIth nerve paralysis (106-271). However, the specialist recommended an evaluation to rule out multiple sclerosis (MS), which was not done. Thus, in this analysis it will be considered a new-onset AESI.
    - One subject (132-154) reported two potential AESIs. Clinical Sjogren's syndrome was diagnosed by the rheumatologist, but appears to be long-standing. Raynaud phenomenon, also reported as an AESI, was noted by the rheumatologist, but information regarding onset is not provided. For this analysis, Raynaud phenomenon will be considered a new-onset AESI because sufficient evidence was not provided by the Applicant to determine it was not.
- The clinical reviewer does not agree with the SEAC that the event of granulomatous dermatitis was not autoimmune, and considers this event a new-onset, potentially immune-mediated event.
- One event of hypothyroidism in the Heplisav-B group (138-141) and two events in the Engerix-B group (112-170, 126-098) were diagnosed by the subjects' physicians without sufficient information available to fully rule out the diagnosis. Based upon information provided by the Applicant in the February 2017 CR response, subject 103-108, who received Heplisav-B and reported hypothyroidism, is no longer assessed as a new-onset AESI.
- The following events were confirmed by the SEAC to be autoimmune or are AESIs, without sufficient information for the clinical reviewer to determine them to be definitely pre-existing: Graves' disease (114-027), ulcerative colitis [proctitis] (122-076), and systemic lupus erythematosus (129-084) in the Heplisav-B group and lichen planus (101-181) in the Engerix-B group.
- One event of lichenoid drug eruption in the Engerix-B group (103-119) was determined by the SEAC not to be autoimmune, but is considered by the reviewer to be a new-onset potential immune-mediated event in this analysis.

In conclusion, in this analysis, the clinical reviewer determined that there were 18 new-onset AESIs in 17 subjects in the Heplisav-B group – Bell's palsy in five subjects, hypothyroidism in two subjects, ulcerative colitis in two subjects, VIth cranial nerve paralysis in two subjects (one was actually insufficiently evaluated for MS), and alopecia areata, polymyalgia rheumatica, IIIrd cranial nerve paralysis, Raynaud phenomenon,

Graves' disease, systemic lupus erythematosus, and granulomatous dermatitis in one subject each – and 5 new-onset AESI in 5 subjects in the Engerix-B group (hypothyroidism in two subjects, and Bell's palsy, lichen planus, and lichenoid drug eruption in one subject each). Of these events 16 events in 16 subjects in the Heplisav-B group (Bell's palsy in five subjects, hypothyroidism in two subjects, ulcerative colitis in two subjects, and alopecia areata, polymyalgia rheumatica, VIth cranial nerve palsy/rule-out MS, Raynaud phenomenon, Graves' disease, systemic lupus erythematosus, and granulomatous dermatitis in one subject each) and five events in five subjects the Engerix-B group (hypothyroidism in two subjects, Bell's palsy, lichen planus, and lichenoid drug reaction) did not have clear alternative plausible causes.

Brief narratives are presented for events that were determined to be autoimmune events and for potential AESIs noted in the summary assessments above, particularly where there was some disagreement between the SEAC and the clinical reviewer or additional information was requested. Narratives for AESIs for Bell's palsy are not presented. None of the Bell's palsy diagnoses were in question and the SEAC considered none of them autoimmune, although they were all new in onset and considered AESIs by the clinical reviewer.

Narratives of new-onset autoimmune AEs

Subject 136-200 was a 47-year-old woman with no history of gastrointestinal symptoms. She was diagnosed with ulcerative colitis following vaccination with symptom onset reported approximately two months following the second vaccination.

Reviewer comment: *The reviewer agrees with the SEAC's assessment that the event was a new-onset autoimmune event. The SEAC determined that there was < 50% likelihood the event was caused by the vaccine, noting that it was likely the subject had an autoimmune process ongoing prior to the onset of symptoms, and prior to vaccination, and that there are no other known associations of any vaccine with inflammatory bowel disease (IBD). However, the 1018 adjuvant is not contained in any other licensed vaccine. In the clinical reviewer's opinion, it is difficult to determine that any one event is caused by vaccination. The fact that AESIs likely occur in subjects that are susceptible, does not indicate that vaccination could not have contributed to the event.*

Subject 108-013 was a 53-year-old woman with no relevant medical history. She was diagnosed with alopecia areata and referred to a dermatologist approximately 7.5 months following last active injection of study vaccine. The subject's mother had a history of alopecia areata. The SEAC assessed the event as a new-onset autoimmune disorder and as not related to study vaccine due to the positive family history, the incidence of the disease in the subject's gender and age group, and the temporal relationship between vaccination and the event.

Reviewer comment: *The reviewer agrees with the SEAC's assessment of the event as a new-onset autoimmune disorder, but notes that an assessment of the relationship between any one autoimmune event and vaccination is difficult.*

Subject 126-038 was a 69-year-old man with type 2 diabetes, hypertension, high cholesterol, left torn rotator cuff status-post surgery, and left shoulder tendonitis and arthritis. On a laboratory draw approximately eight months after the second dose, the subject was noted to have an elevated ESR (71 mm/hr), as well as WBC of 14,600/µL,

platelet count 442,000/µL, a hemoglobin of 10.9 g/dL, and a negative rheumatoid factor (RF) and anti-nuclear antibody (ANA). A bone marrow biopsy reportedly showed no significant abnormality and a chest and abdomen CT scan showed diverticulosis. Approximately one month later, the subject was evaluated by a rheumatologist for a four-month history of hip and back pain, and a longer history of shoulder pain. He was diagnosed with polymyalgia rheumatica, which responded to steroids. Following the Week 56 visit, at a visit for a flare in symptoms, the rheumatologist noted "there was no evidence of temporal arteritis or underlying rheumatoid arthritis."

Reviewer comment: The SEAC's assessment of the event as a new-onset autoimmune disorder is reasonable. The SEAC assessed the event as not related to vaccination given the long interval between vaccination and diagnosis and prevalence of the disease in the subject's age group. However, the reviewer notes that the subject reported symptom onset approximately five months following vaccination the second vaccination. In the opinion of the clinical reviewer, the temporal association is moderate and there is no clear alternative cause.

Subject 136-149 had elevated TSH (7.15 mIU/L, normal range 0.45-4.50) and anti-TG antibody (1060 IU/mL, normal range 0.0 - 40.0) noted following vaccination. Subject was ultimately diagnosed with papillary thyroid carcinoma with Hashimoto's thyroiditis. Pre-vaccination study laboratory draw showed normal TSH and anti-TPO antibody. Baseline anti-TG does not appear to have been tested.

Reviewer comment: *The SEAC's adjudication of the event as a new-onset autoimmune event with an alternative plausible cause of thyroid cancer is reasonable. The narrative submitted states that the SEAC noted the Week 28 laboratory assessment was written in their narrative as if the results were from baseline. In 125428/0.74, in response to item 33 in the 10 November 2016 CR, the Applicant noted this was an isolated incident, it was identified by the SEAC because source documents were submitted to the SEAC as part of the "autoimmune package" they received, and it was corrected quickly.*

<u>Narratives of additional selected potential AESIs in the Heplisav-B group</u>
Subject 103-108 had elevated thyroid stimulating hormone (TSH) (4.83 mIU/L, normal range 0.45 - 4.50) and normal free T4 noted on routine assessment six months following dose 2 of Heplisav-B. Levothyroxine was started by the subject's primary care physician. Pre-vaccination study laboratory draw showed normal TSH (3.64 µIU/mL, normal range 0.34-5.60) and free T4. The investigator did not agree with the primary care physician's diagnosis of hypothyroidism. However, the subject declined evaluation by an endocrinologist and further laboratory assessment of hypothyroidism. In 125428/0.74, the Applicant provided results of banked serum samples drawn during the study. They showed normal TSH at Week 0 and 24, elevated TSH at Week 28 (5.26 mU/L, approximately one month prior to the TSH noted on routine assessment), normal free T4 at all time points, and no abnormalities in anti-thyroid peroxidase antibodies (anti-TPO) and thyroid stimulating immunoglobulin (TSI) at all time points.

Reviewer comment: *Although some patients have overlap between autoimmune thyroiditis and Grave's disease, in this subject, it is unclear why the Applicant assessed TSI instead of anti-thyroglobulin (anti-TG) antibodies. The subject has two elevated TSH values approximately six weeks apart and normal free T4, indicative of subclinical hypothyroidism. As approximately 90 – 100% of subjects with autoimmune thyroiditis have anti-TPO antibodies, and the subject had negative anti-TPO at the time of elevated*

TSH, the reviewer considers this a new-onset, autoantibody negative subclinical hypothyroidism and not an AESI.

Subject 138-141 was a 44-year-old woman diagnosed with hypothyroidism by her PCP approximately 7.5 months following dose 2 and treated with levothyroxine. No laboratory results were available. Analysis of pre-vaccination and Week 28 (two months prior to diagnosis) study laboratory draw showed normal TSH, anti-TPO, and anti-TG antibodies. The subject declined site access to medical records and referral to a specialist. The SEAC assessed the hypothyroidism as not autoimmune.

Reviewer comment: *Information on the diagnosis of hypothyroidism is limited. The subject had normal TSH and no thyroid autoantibodies two months prior to this diagnosis. However, for this analysis, the event will be considered a new-onset AESI, assuming the treating physician's diagnosis was correct and because no information was submitted to definitively rule out a diagnosis of autoimmune hypothyroidism (for example laboratory results at the time of or after the diagnosis was made indicating no hypothyroidism or no autoantibodies).*

Subject 112-326 had an elevated TSH (9.06 µIU/mL, normal range 0.50 - 6.00) that was noted one year following vaccination with negative anti-TPO and anti-TG antibody. Analysis of pre-vaccination study laboratory draw showed normal TSH and negative anti-TPO. In 125428/0.74, in response to 10 November 2016 CR item 34, the Applicant provided the specialist's note, prior to having results of the thyroid autoantibody testing, in which the specialist stated that of the etiology of the hypothyroidism was unspecified.

Reviewer comment: *The SEAC's assessment that the hypothyroidism is a new-onset event that is not autoimmune appears reasonable, but another explanation for the hypothyroidism is not provided by the Applicant. This event is not counted by the reviewer as an AESI.*

Subject 114-027 was a 55-year-old man with a seven-year history of osteoporosis, dyslipidemia, benign prostatic hyperplasia, and suspected Gilbert's syndrome who had low TSH (0.23 µIU/mL, normal range 0.4-6.0) and two positive TSI results (435-647%, normal range < 140) results noted approximately six weeks following dose 2 of Heplisav-B. Anti-TPO and anti-TG were negative at that time. Pre-vaccination laboratory results over the prior eight years showed TSH generally in the low range of normal (0.39 – 0.56 µIU/mL, normal range 0.4 - 6.0). The subject also had a family history of hyperthyroidism. The narrative states that the endocrinologist assessed that the pre-vaccination laboratory results suggested subclinical hyperthyroidism and that it was possible the subject "had had mild Graves' disease for some time." The subject was treated with methimazole. Analysis of pre-vaccination study laboratory assessment showed the subject had TSH within normal limits and negative anti-TPO. In 125428/0.74, in response to item 34 of the 10 November 2016 CR, the Applicant stated that the baseline serum sample was exhausted and unable to be tested for TSI. The SEAC assessed the event as a pre-existing autoimmune event.

Reviewer comment: *The reviewer agrees with the SEAC's assessment that the event is autoimmune. The specialist and the SEAC agreed that the laboratory evidence and history of osteoporosis indicated the hyperthyroidism (possibly subclinical) was long-standing. The reviewer identified no other apparent cause for the osteoporosis. However, a baseline TSI could have definitively determined if the condition was pre-*

existing. While, the SEAC and specialist's assessment of the pre-existing nature of the AESI is not unreasonable, for the purposes of this analysis, the reviewer considers this event to be new in onset as the definitive evidence to establish pre-existence was not provided.

Subject 133-107 had low free T4 (0.76 ng/dL, normal 0.77 - 1.61) reported approximately 7 months following dose 2 of Heplisav-B. He was diagnosed with hypothyroidism based on this result. There is a discrepancy between the narrative and the datasets, but based upon information provided in 125428/0.74, in response to 10 November 2016 CR item 34, it appears that the subject was started on levothyroxine at that time, consistent with information in the dataset. Follow-up laboratory assessment three weeks later, presumably on levothyroxine, showed low TSH (0.21 µIU/mL, normal range 0.34 - 4.82), and normal free T4 (0.96 ng/dL, normal range 0.77 - 1.61). The subject was evaluated by an endocrinologist for hypothyroidism. Anti-TPO and anti-TG were negative and a thyroid ultrasound showed multinodular goiter. Analysis of pre-vaccination, Week 24, and Week 28 (11 days before the hypothyroid diagnosis) study laboratory assessment showed normal TSH, anti-TPO, and TSI. The investigator retracted the event of hypothyroidism as a potential AESI and changed the event to normal thyroid function.

Reviewer comment: *On multiple tests, shortly before and after the diagnosis of hypothyroidism, there is no evidence of thyroid autoantibodies, nor clear evidence of thyroid function abnormality. The SEAC's assessment that the event is not autoimmune is appropriate.*

Subject 122-076 was a 33-year-old man who was hospitalized with pseudomembranous colitis approximately three months following the second vaccination. A colonoscopy at that time could not rule out ulcerative colitis. Reports of a flexible sigmoidoscopy at approximately the same time showed ulcerative proctitis. The narrative states that a reference was made in the medical records to a colonoscopy and esophagogastroduodenoscopy performed one year prior to the recent procedures that "inferred that a diagnosis of inflammatory bowel disease was made." The subject denied a history of IBD prior to enrollment and rescinded permission to view his medical records.

Reviewer comment: *The chronology of disease presentation and diagnosis is unclear. SEAC's assessment was that the event was a pre-existing autoimmune event. However, as the subject reports diagnosis occurred following vaccination and per the narrative the records appear inconsistent, for this analysis, the AESI is not considered pre-existing.*

Subject 134-228 was a 69-year-old man with a history of fibromyalgia, lumbar spondylosis, and chronic back pain status post lumbar fusion. He was hospitalized for pneumonia and his stay was prolonged due to severe headaches with diminishing vision in his left eye. A history of eye pain prior to study enrollment was reported. He had a non-contrast CT of his brain at admission, which was within normal limits. During hospitalization, bilateral temporal artery biopsies were negative for signs of active or healed vasculitis. He received a course of steroids, initiated during hospitalization, because of the constellation of intermittent headaches with diminishing vision, a reportedly elevated ESR and CRP, chronic myalgias, and concern for temporal arteritis. Myalgias were reported as an AESI. He was not seen by a neurologist or an

ophthalmologist during his hospital stay. The Applicant reports that multiple physical exams indicate that he had a normal cranial nerve exam with no mention of visual deficits. His hospital discharge summary attributed the headache to pneumonia and noted it had resolved at discharge. During the hospitalization, he was also evaluated for anemia (thought due to chronic disease) and neutropenia (thought due to infection or medications).

Upon follow-up with his rheumatologist, he complained of back and hip pain and had an elevated ESR and CRP at that time. He received another course of steroids (datasets indicate to treat finger and foot pain). At the Applicant's request, he was evaluated by another rheumatologist, who assessed the subject as having myalgias and polyarthralgia due to spinal disease (history of prior back surgeries) and fibromyalgia, leukopenia, and thrombocytopenia without evidence of autoimmune disease. A laboratory draw at that time showed a normal ESR, CRP, and autoantibody panel.

Reviewer comment: *CBER requested further information regarding the headaches and visual changes leading to the temporal artery biopsy in the 9 September 2016 IR. The additional information submitted by the Applicant is reflected in the narrative above. This subject reported headaches and diminished vision and although an evaluation for an immune-mediated condition was negative, except for a transient increase in ESR and CRP, the subject was treated with and responded to steroids. While there is no definitive diagnosis of an immune-mediated process, symptoms of acute visual loss that appeared to require and respond to steroids and the lack of a definitive or alternative plausible diagnosis is concerning for an undiagnosed immune mediated process.*

Subject 129-084 was a 62-year-old woman with a history of bilateral hand osteoarthritis for nine years and a family history of ankylosing spondylitis. Approximately 1.5 months following last active injection, she developed worsening hand pain. She was evaluated by a rheumatologist who noted signs of joint inflammation and assessed her as having systemic lupus erythematosus (SLE). Laboratory results at the time of diagnosis included ANA 1:640 (normal range < 1:40), homogenous pattern, leukopenia, anemia, double stranded DNA antibody 25 IU/mL (normal < 5), positive Sjogren's antibody (SS-A), positive ribosomal P antibody, and negative Smith, RF, cyclic citrullinated peptide (CCP) antibodies, SS-B, and remainder of the autoantibody panel. Analysis of pre-vaccination study laboratory assessment showed a positive ANA 1:160, homogenous pattern and negative double stranded DNA (90 IU/mL, negative < 100). The SEAC assessed the event as a pre-existing, though asymptomatic, autoimmune disease, based on the positive ANA at baseline, and considered the event an evolving connective tissue disease most consistent with lupus.

Reviewer comment: *The SEAC's assessment is reasonable. However, following vaccination, the subject appears to meet diagnostic criteria for SLE. Prior to vaccination, no hematology is reported and anti-ds DNA is at the high limit of normal. In addition, she reported acute worsening of symptoms and further elevation in an abnormal ANA following vaccination. It is possible the vaccine worsened the pre-existing condition or that it contributed to the development of SLE in a susceptible subject. For this analysis, the subject with be considered to have a new-onset AESI because of the acute onset of symptoms and positive diagnostic criteria following vaccination.*

Subject 132-154 was a 54-year-old woman with a possible history of fibromyalgia was evaluated for Sjogren's syndrome four months following last active vaccination, based

upon concerns of her primary care physician and ophthalmologist. She reported symptoms of dry eyes and mouth for 6-7 years prior to study enrollment. Extractable nuclear antigen screen was negative for SSA, SSB, Smith, RNP, SCL-70, and Jo-1. ESR, RF, and serum protein electrophoresis were normal. The rheumatologist assessed her as having a clinical diagnosis of Sjogren's syndrome and symptoms of Raynaud phenomenon in her toes. No further details, including onset, is given for Raynaud phenomenon. The rheumatologist noted that a lip biopsy was needed for definitive diagnosis of Sjogren's, but the subject opted for empiric treatment instead. The subject discontinued the first line treatment due to side effects and the symptoms were reported as ongoing at study conclusion. The SEAC assessed the events of Sjogren's syndrome and Raynaud phenomenon as not autoimmune events, noting that the subject's sicca symptoms were pre-existing.

Reviewer comment: *The clinical reviewer agrees with the assessment that the sicca symptoms were pre-existing and are not reported as worsening following vaccination. However, the Applicant has not provided any evidence to determine whether the subject's Raynaud was pre-existing or new-onset and thus, it will be considered a new-onset AESI for this analysis.*

Subject 102-163 was a 45-year-old woman who reported left shoulder and neck pain with finger paraesthesia approximately ten months following the last active injection. She was evaluated in an emergency room, received an X-ray, and was reportedly diagnosed with rheumatoid arthritis. No treatment was given. Four months later, she was evaluated by a rheumatologist who diagnosed impingement syndrome based on history, physical, and X-rays of multiple joints without evidence of inflammatory arthropathy. ANA was positive (1:320, normal range < 1:80) and CRP was elevated (9.9 mg/L, normal 0 – 4.9), but the remainder of the autoantibody tests were negative, including anti-RF and anti-CCP. Analysis of a pre-vaccination study laboratory draw showed a negative ANA.

Reviewer comment: *The SEAC's assessment of the event as not an autoimmune event is reasonable and consistent with the specialist's assessment. The clinical reviewer agrees with the SEAC's notation that there may be an underlying autoimmune disorder developing, particularly as the subject's ANA became positive following vaccination. But at the time of evaluation, after Week 56, there was not clear clinical evidence for diagnosis of an autoimmune event.*

Subject 117-119 was a 50-year-old man whose history included hypertriglyceridemia and type 2 diabetes. Prior to study initiation, he was stable on metformin, pitavastatin, and fenofibrate. Unintentional weight loss, and possibly polyuria and polydipsia, are noted beginning two months after second vaccination. The subject reported double vision (PT = diplopia, first AESI) with mild headache three months following vaccination. Five months after dose 2, his cholesterol (761 mg/dl, normal range 125-200), triglycerides (6266 mg/dL, normal <150), and HbA1c (12.2 %, normal <5.7%) were noted to be markedly elevated. Hypertriglyceridemia was considered serious because it was life-threatening. His medications were adjusted and he began insulin. He was treated as an outpatient and no follow-up laboratory assessments are provided. He was evaluated by a neurologist at the time of his laboratory abnormalities, who noted mild third or fourth cranial nerve palsy, suspected to be due to his uncontrolled diabetes. The neurologist noted he did not have cavernous sinus thrombosis. Seventeen days after the laboratory abnormalities and ten days after insulin initiation, he reported Bell's palsy

(second AESI). Upon evaluation by the neurologist one week later, the subject reported the diplopia had resolved "with correction of his high blood sugar levels," however, glucose was noted to be 400's at that time. The neurologist suspected the Bell's palsy was also due to uncontrolled diabetes. The event of dyslipidemia was considered resolved at this time when the subject was seen by the investigator (no labs provided). A neuro-ophthalmologist evaluated the subject approximately two weeks later. He attributed the third nerve palsy to diabetes and assessed the seventh nerve palsy as not related to vaccine. The SEAC assessed both events as not autoimmune disorders and not related to vaccine. The SEAC was not required to determine relationship as they did not assess the events as autoimmune. But in the narrative, the SEACs's summary and assessments state three times (assessments of neurologist, neuro-ophthalmologist, and SEAC) that the paralytic strabismus/oculomotor palsy was thought due to diabetes, without specifically attributing the Bell's palsy to diabetes.

Reviewer comment: *The subject had a mild third cranial nerve palsy (diplopia) at the time of significant laboratory abnormalities and Bell's palsy when the metabolic abnormalities were being treated, though glucose remained high. The reviewer agrees that the subject's uncontrolled diabetes is a plausible cause of the third nerve palsy. The exact cause of the Bell's palsy is unknown. The reviewer agrees that it is possible diabetes contributed to the event. However, taking into account the assessments of the specialists and SEAC, the reviewer does not consider diabetes as a likely alternative plausible cause. Furthermore, the Applicant identified this event of Bell's palsy as a new-onset AESI. Both events are considered AESIs. Of note, the PT for this event is diplopia, which is not included in list of AESIs. As a consequence, the event of diplopia is not considered in several of the Applicant's analyses of AESIs in the CSR and the integrated Clinical Summary of Safety.*

Subject 106-271 was a 43-year-old man with a history of head injury and loss of consciousness 20 years previously, who was seen in the emergency room for right foot drop approximately four months following dose 2. One week later, he reported diplopia (noted in the narrative later to be right sided) and resolved foot drop. The emergency room visit note is contradictory, apparently noting "extraocular movements intact in the right eye" and an "obvious 6th cranial nerve palsy." A CT of the head was normal. Findings were discussed with a neurologist and the subject was not admitted. A brain MRI showed a "mild to moderate degree of nonspecific T2 white matter hyperintensities clearly pathologic and unusual for the subject's age." Eleven days after the diplopia was evaluated, symptoms had at least partially resolved and a normal cranial nerve exam was noted by the subject's PCP. He was evaluated by a neurologist approximately two months later, reporting dysphagia, but no more foot drop or diplopia. The neurologist recommended a lumbar puncture to evaluate for MS, but the subject declined, noting that his symptoms had resolved. The SEAC assessed the event as not an autoimmune event. The SEAC also noted that giant cell arteritis or vasculitis could cause a sixth cranial nerve palsy, but symptoms would be unlikely to be transient with no other abnormalities.

Reviewer comment: *The clinical reviewer agrees with the SEAC that the VIth cranial nerve palsy is unconfirmed as only one note appears to mention it and that note also contradicts the finding. While there is no laboratory evidence of MS, for the purposes of this analysis, the clinical reviewer does not consider that this diagnosis was adequately ruled out, given the neurologist's recommendations.*

Subject 134-064 was a 49-year-old man with a ten-year history of diabetes, which was poorly controlled (HbA1c 10% 4.5 months prior to the event), dyslipidemia, and hypertension, reported left-sided diplopia following vaccination. He was evaluated by his PCP and an ophthalmologist who diagnosed VIth cranial nerve palsy. ESR and CRP were normal. Brain MRI showed non-specific bilateral lesions, possibly related to microvascular ischemic white matter disease. His ophthalmologist recommended control of his medical conditions. Symptoms resolved approximately two months later. He was then evaluated by a neurologist, who attributed the resolved diplopia to microvascular disease and diabetes. The SEAC adjudicated the event as not autoimmune.

Reviewer comment: *The reviewer considers this event a new-onset AESI with an alternative plausible cause of microvascular disease and diabetes.*

Subject 131-035 was a 43-year-old Hispanic female subject with a history of obesity, hypertension, rosacea, and bilateral ankle cellulitis for which she was hospitalized twice 2-3 months prior to study enrollment. She reported a rash of her shins and forearms 97 days following first vaccination and 69 days following second. As per the datasets, she was initially treated with amoxicillin and naproxen. After 13 days of treatment, her primary care physician diagnosed her with erythema nodosum and treated her with oral steroids. She was evaluated two days later by a dermatologist and a biopsy of her forearm demonstrated non-caseating granulomatous inflammation. Shin biopsy was nonspecific. She reported that a tuberculin skin test and chest X-ray were normal but no information about the timing or reason for those studies is reported. The rash initially improved with steroids but followed a recurring course over the next several months. She continued to deny systemic symptoms. A repeat skin biopsy again demonstrated granulomatous dermatitis with an interstitial pattern (staining negative for fungus and mycobacteria); differential diagnosis per the dermatopathologist was sarcoidosis, coccidioides, and granuloma annulare. Her primary care physician treated the rash with a prednisone taper and told her to discontinue her blood pressure medications (valsartan and hydrochlorothiazide, both started seven days prior to study initiation) in case it was a drug reaction. As per the datasets, she continued these medications. Her only other concomitant medication was depo-provera. An angiotensin converting enzyme level was elevated (86 U/L, normal range 9-67). Coccidioides antibody complement fixation was negative. The subject's insurance company refused a pulmonary consult and chest computed tomography (CT) and consequently, the subject declined these evaluations. The rash was reported as resolving at the study conclusion, but also intermittent and ongoing 10 months following its onset, as per the narrative. The SEAC adjudicated the event as not autoimmune, noting there was not a clear evolution of the rash, the subject experienced differing types of rash, and it was not responsive to two different types of steroids.

In the September 9, 2016 IR, CBER asked the Applicant to provide their rationale for not pursuing a complete evaluation to rule out a systemic granulomatous disease in this subject. In 125428/0.67, they responded that they "attempted to have the condition further evaluated and offered to cover the costs of the chest CT and pulmonary consultation but the subject refused both appointments."

Reviewer comment: *Etiology and chronology of the rash on the lower extremities is unclear. However, the rash on the upper extremities is granulomatous and appears to be new in onset, as noted by her primary care physician in the narrative. Sarcoidosis*

was a leading differential diagnosis as per the dermatopathologist and was not ruled out. Granulomatous dermatitis has been described as one entity in the spectrum of autoimmunity-related granulomatous dermatitis,[45, 46, 47] a rare condition (unknown incidence) with case reports and series in the literature. It is often associated with an underlying immunoreactive condition diagnosed previously or concurrently, but rarely reported when the underlying systemic disease is not known. Autoimmunity-related granulomatous dermatitis has been associated with connective tissue disorders, such as systemic lupus erythematosus and rheumatoid arthritis, GPA, antiphospholipid antibody syndrome, and malignancy.[45 47] Further investigation for autoimmune diseases in this subject was not conducted. Interstitial granulomatous drug reactions have been reported in association with angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, and furosemide.[48, 49] The suggestion of a drug reaction is reasonable, but also appears to have come from the primary care physician and not the dermatopathologist examining the biopsy. The clinical reviewer considers this event a new-onset potentially immune-mediated event, concerning for an additional granulomatous disease in the Heplisav-B safety database.

Subject 131-109 was a 49-year-old U.S. Hispanic man with a relevant history of type 2 diabetes, cerebrovascular disease, cardiovascular disease, hypertension, morbid obesity, gastric bypass surgery, fatty liver disease, former smoker, and alcohol user (few times a month). Following gastric bypass surgery in 2010, the subject's BMI decreased from 45 kg/m2 to 34.1 kg/m^2 at study enrollment and he was able to control his hyperglycemia with diet and exercise instead of metformin, which he was previously taking. Family history included Crohn's disease. Nine years prior to study enrollment, he was diagnosed with a transient ischemic attack (TIA) versus lacunar infarct, age-indeterminate left thalamic infarct.

Two months after receiving the second dose of study vaccine, he was hospitalized for an acute thalamic infarct. A computed tomography angiography (CTA) of the chest was performed to evaluate the incidental findings noted on imaging of the head and neck, which demonstrated "smooth, concentric mural thickening of the aortic arch," concerning for a large vessel vasculitis. Erythrocyte sedimentation rate (ESR) was 33 mm/hr (normal 0-20) and a high-sensitivity C-reactive protein (CRP) was 2.8 mg/L (no normal range provided). With the exception of a chest x-ray performed four years earlier, which was reported by the Applicant as normal, there are no known prior imaging studies of the subject's chest. At the Applicant's request, the subject received multiple subsequent imaging studies, each demonstrating stable mural thickening. A rheumatologist diagnosed him with Takayasu arteritis. The SEAC assessed the events as not autoimmune and questioned the diagnosis of Takayasu arteritis.

Reviewer comment: *Because of the possibility of a new-onset granulomatous vasculitis in the Heplisav-B group, the CBER obtained two consults, regarding this case – one rheumatologist and one cardiac imaging specialist. Both consultants agreed the most likely diagnosis was Takayasu arteritis, but that the disease was likely chronic, beginning prior to study enrollment. The Applicant, in consultation with external consultants, proposes aortic intramural hematoma. Per the clinical reviewer's discussion with CBER's cardiac imaging consultant on 25 May 2016, the CBER consultant did not consider the Applicant's proposed diagnosis plausible based upon evaluation of imaging.*

In response to the 9 September 2016 IR requesting any further analyses on the differences in AESIs between groups, the Applicant provided follow-up regarding this

subject in 125428.0.67. The subject saw his primary care physician 23 months following the original CTA and reportedly had no signs or symptoms of Takayasu arteritis.

Narratives of additional selected potential AESIs in the Engerix-B group

Subject 112-170 was a 71-year-old woman whose medical history included depression and high cholesterol. Of note, the narrative appears to report that she had a history of pernicious anemia, of which she was unaware, and that she was on vitamin B12, neither of which are recorded in the datasets. She was diagnosed with celiac disease, for which she was evaluated six days after dose 1 at which time she reported long-standing symptoms. Celiac disease was assessed as a pre-existing autoimmune event. Two and a half months after dose 3, an elevated TSH (5.34 mU/L, normal range 0.45 - 4.50) and normal free T4 was noted in the setting of evaluation for fatigue and levothyroxine was started. Analysis of pre-vaccination study laboratory draw showed TSH (4.56 uIU/mL, normal range 0.34-5.60) within normal limits and negative anti-TPO and anti-TG. The subject declined referral to an endocrinologist and no thyroid autoantibody testing was reported following diagnosis of hypothyroidism. Analysis of Week 24 (2.5 months prior to diagnosis) and Week 28 (almost two months prior to diagnosis) study laboratory draw, performed by the Applicant, showed negative anti-TPO and anti-TG at Week 24 and negative anti-TPO at Week 28. The SEAC appears to question the diagnosis of hypothyroidism as it was based on one mildly abnormal TSH. They assessed the hypothyroidism as not autoimmune based upon incomplete information.

Reviewer comment: *As the treating physician's diagnosis is hypothyroidism and limited information is available, for this analysis the event will be considered a new onset AESI. No information was submitted to definitively rule out the diagnosis, such as negative antibodies at the time of TSH elevation.*

Subject 126-098 was a 58-year-old woman who had an elevated TSH (4.45 uIU/mL, normal range 0.27-4.20) noted on routine testing four months following the third dose of Engerix-B. The subject was started on levothyroxine. Analysis of pre-vaccination study laboratory draw showed TSH (4.17 uIU/mL, normal range 0.34-5.60) within normal range and negative anti-TPO. Subject declined expert consultation and declined to release any further information regarding the hypothyroidism. No Week 24 and 28 testing is reported. No thyroid autoantibody testing was reported following diagnosis of hypothyroidism. The SEAC questioned the diagnosis, given the borderline TSH and normal free T4, and assessed the hypothyroidism as not autoimmune.

Reviewer comment: *Limited information is available and no antibody testing was performed concurrently with or following the elevated TSH. As the treating physician's diagnosis is hypothyroidism, for this analysis, the event will be considered a new onset AESI*.

Subject 101-181 was a 63-year-old man with no relevant past medical history who was evaluated by a dermatologist for several skin lesions 25 days following dose 1. An "asymptomatic" rash of erythematous papules with trailing scale on the lower back, which was improving somewhat with betamethasone, was observed. The subject reported the rash had been present for two months. He had not reported the rash, nor was it evaluated at screening. Pityriasis rosea was diagnosed. The next report of a rash in the narrative was approximately seven months later. The subject reports this rash on his back was "similar to the one that he's had before," but the dermatologist's note states it had a different appearance. Upon reevaluation by the dermatologist, and based upon

a biopsy, he was diagnosed with lichen planus. The SEAC assessed the event as a pre-existing autoimmune event.

Reviewer comment: *While the SEAC's assessment is reasonable, the start date of the rash is in question. The subject reports the lichen planus rash was similar to the rash that pre-dated study enrollment. The investigator reported the rash onset at day 117 following dose 3. The reason for selecting this particular date is unclear as it appears to be after the primary care physician reevaluation and before the dermatologist's reevaluation of the rash. However, because, with this start date the investigator appears to suggest it is a distinct rash, the dermatologist evaluates it as having a distinct appearance, and a significant time passed between reports of the rash, the clinical reviewer considers this autoimmune event to be new in onset for this analysis.*

Subject 103-119 was a 66-year-old man, with a relevant medical history of stroke with left foot drop, lumbar degenerative joint disease, lumbar radiculopathy, peripheral neuropathy, bilateral chronic knee pain, and chronic fatigue syndrome, and taking aspirin (4 years), benazepril (5 years), amlodipine (12 years), tramadol (4 years), and famotidine (2 years). He reported a trunk rash approximately seven weeks following dose 3 of Engerix-B, assessed as a "bullous dermatitis" by his PCP and treated with oral prednisone and cephalexin. Approximately three weeks later, his PCP determined his rash had improved and assessed it as guttate psoriasis, prescribing an oral prednisone taper. Also at this visit, he reports left foot pain, which appears to be different than his previously reported pain. Following oral steroids, he was prescribed topical steroids, and also started gabapentin for peripheral neuropathy, which was continued for the remainder of the study. The subject was evaluated by a dermatologist, who noted a resolving unspecified dermatitis, consistent with a drug reaction. Biopsy showed small foci of lichenoid lymphocytic infiltrates, or "patchy lichenoid dermatitis" (verbatim term). Differential diagnosis included drug eruption, pityriasis lichenoides, and connective tissue disease. The rash was considered to be clearing and no further medications were prescribed to treat it. The dermatologist indicated that the event was a suspected drug reaction and possibly related to study vaccine. The investigator confirmed no other medications were started by the subject during the study prior to the start date of the rash. The rash was considered resolved 117 days after it was reported. The SEAC assessed the rash as not an autoimmune disorder, with one member noting that it was possibly, though unlikely, autoimmune. In contrast to the dermatologist, the SEAC determined the event was unlikely to be due to study vaccine, given that the event occurred 191 days following second vaccine dose and that it was more likely to be due to other medications the subject was taking, which had been described to cause skin lesions.

Reviewer comment: *Presumably, the SEAC's assessment of relationship refers to the event's relationship to Heplisav-B only, as the rash is reported within two months of the third dose of Engerix-B. The event could represent a drug reaction, pityriasis lichenoides, or a connective tissue disorder, though this may be less likely given its resolution without ongoing treatment and no clear onset of other symptoms. Assuming the etiology is as the dermatologist assessed it, a lichenoid drug reaction, similar drug reactions have been described in association with several of the subject's medications. While such reactions have been described to have a latency period of months up to years, the subject reports taking all of these medications for at least two years. In addition, the rash seems to have resolved without discontinuation of these medications. Lichen planus has been reported in association with Hepatitis B vaccine and infection,*

and is likely associated with the antigen.[50] The rash was reported after the third and final dose, so there is no way to determine if the rash would have reappeared with additional exposure. While, the SEAC correctly notes that this event is not autoimmune, the clinical reviewer considers this event may be a new-onset potentially immune-mediated event for this analysis.

Reviewer comment: *In summary, the SEAC adjudicated four events as new-onset autoimmune events in the Heplisav-B group and no events in the Engerix-B group, noting that one event was concurrent with and possibly caused by another diagnosis (hypothyroidism due to papillary thyroid carcinoma). An additional five subjects in the Heplisav-B group and one subject in the Engerix-B group reported Bell's palsy, an AESI, and a diagnosis that was not in question in any of the cases. All of these events were relatively common AESIs, such that their occurrence in a study of this size was not unlikely, though the incidence of Bell's palsy was slightly higher than expected in the Heplisav-B arm (5 events in 5587 subjects = 89 subjects per 100,000 persons versus up to 34 per 100,000 persons per year in the U.S.).[43]*

In the reviewer's analysis, in which diagnosed conditions referred to the SEAC were generally considered AESIs until proven otherwise, 16 subjects in the Heplisav-B group (0.3%) and 5 subjects in the Engerix-B group (0.2%) were identified as having new-onset AESIs without clear alternative plausible causes. In general, the reviewer considers the SEAC's assessments to represent a less biased (in other words, blinded) assessment of AESIs, but disagrees with the use of a strict definition of autoimmune, as events can be immune-mediated and not necessarily autoimmune. Many of the events that were added in the reviewer's analysis were events in which the diagnosis was questionable (for example, all cases of hypothyroidism were mild elevations of TSH without evidence provided of abnormal free T4), highlighting the difficulty with evaluating AESIs even when collection of events is prospectively specified. The reviewer specifically disagrees with the SEAC's assessment of granulomatous dermatitis and considers it an autoimmune disease of the skin with potential overlap with other systemic granulomatous diseases reported in association with Heplisav-B (GPA and Tolosa-Hunt syndrome) in previous trials.

MAEs in three subjects (one each with granuloma annulare, pyoderma gangrenosusm, and anaphylaxis) were initially evaluated by the clinical reviewer as potentially immune-mediated, but are not on the list of AESIs and were not referred to SEAC. In 125428/0.74, in response to November 2016 CR item 38, the Applicant submitted additional information regarding these subject's diagnoses. The additional information indicated that these diagnoses were either in question or could be explained by alternative plausible causes.

Thyroid MAEs

Version 4 of the SEAC Charter, dated 18 November 2014 included a change in process for referral of newly identified events of hypothyroidism to the SEAC. After this date, banked baseline sera were first examined and if the subject was determined to have evidence of thyroid disease prior to study vaccination, SEAC did not evaluate the event.

Because the referral procedures changed mid-study, the most common cause of both hypothyroidism and hyperthyroidism in the U.S. is autoimmune, and both clinical states can present as goiter, hypothyroidism or hyperthyroidism, an analysis of all thyroid MAEs is presented in the table below.

Table 40. Thyroid MAEs reported from vaccination through Week 56, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav-B N = 5587 n (%)	Engerix-B N = 2781 n (%)
At least one event	22 (0.4)	13 (0.5)
Hypothyroidism	10 (0.2)	6 (0.2)
Autoimmune thyroiditis	2 (0.04)	2 (0.1)
Basedow's disease (Grave's)	2 (0.04)	2 (0.1)
Goiter	2 (0.04)	0
Hyperthyroidism	2 (0.04)	0
Primary hypothyroidism	0	1 (0.04)
Thyroid mass	0	1 (0.04)
Blood thyroid stimulating hormone abnormal	2 (0.04)	0
Blood thyroid stimulating hormone increased	2 (0.04)	2 (0.1)
Thyroid function test normal*	1 (0.02)	0

Source: Adapted from BLA STN 125428/0.42, CSR DV2-HBV-23, Table 12-12, p. 94.
N = number of subjects in each treatment group
n = number of subjects reporting event
* Subject 133-107 was diagnosed as hypothyroid by his primary care physician. SEAC and investigator ultimately assessed the event as normal thyroid function.

In 125428/0.74, in response to November 2016 CR item 31, the Applicant submitted information about retracted events of thyroid dysfunction. Twelve events were retracted from SEAC adjudication in the Heplisav-B arm and four events in the Engerix-B arm. Three of these events in the Heplisav-B arm were reported as AEs and are reflected in the table above, but were retracted due to the transient nature of the laboratory abnormality. A similar proportion of events in each study arm were retracted based upon baseline laboratory assessment (six events in the Heplisav-B arm and three in the Engerix-B arm) and based on the investigator disagreeing with the initial diagnosis (one in each arm). Two events in the Heplisav-B arm (133-158, 122-248) were retracted because a history of TSH elevation was noted prior to study enrollment despite normal baseline TSH assessment by the Applicant.

Reviewer comment: *Overall, thyroid MAEs occurred at similar rates between both study groups. The reviewer agrees with the retractions that were made in that these events do not appear to be new-onset AESIs.*

6.3.12.6 Clinical Test Results

Subjects enrolled at sites 121 and 140 were eligible for the laboratory sub-study; all but one subject from site 121 participated. Approximately 300 subjects were enrolled in the laboratory sub-study, 207 in the Heplisav-B group and 102 in the Engerix-B group.

Renal function was assessed by serum creatinine and urine creatinine, urine microalbumin, urine microalbumin/creatinine ratio, and urine microscopy for cells, casts, crystals, mucous, bacteria, and yeast. The mean and median serum creatinine levels at baseline and Weeks 4, 8, 24, and 56 in Heplisav-B recipients were similar to that of Engerix-B recipients. An analysis conducted by the reviewer demonstrated that 14 Heplisav-B subjects (6.8%) and three Engerix-B (2.9%) subjects had at least one abnormal serum creatinine and an increase of ≥ 0.2 mg/dL from baseline for at least one

post-vaccination laboratory draw. None of these subjects had MAEs of renal dysfunction reported. One subject had an increase of > 0.5 mg/dL in creatinine noted: a 58-year-old female (121-149) in the Heplisav-B group with a baseline creatinine of 0.9 mg/dL, had an increase to 1.7 mg/dL at Week 56. The mean and median urine microalbumin creatinine measurements were higher for Engerix-B subjects compared to Heplisav-B subjects at baseline and at post-vaccination time points. A similar percentage of subjects (11.6 – 11.8%) in each group had normal baseline urine microalbumin/creatinine ratio with abnormal post-vaccination values. No RBC casts, which could be indicative of specific immune-mediated diseases, were reported.

Reviewer comment: *No clear patterns of renal injury following Heplisav-B were noted in the laboratory sub-study in DV2-HBV-23. There were no differences between study groups identified that would help explain the small imbalance noted in acute and chronic renal failure MAEs noted in Section 6.3.12.2.*

Thrombophilia was assessed by testing subjects for genetic risk factors (Protein C, Protein S, antithrombin III, Factor V Leiden) at baseline and for PT, PTT, and antiphospholipid antibodies (anti-cardiolipin IgG/IgM, anti-beta2 glycoprotein 1 IgG/IgM, and lupus anticoagulant screen/confirmatory) at Weeks 0, 4, 8, 24, and 56.

The mean PT and PTT values, standard deviations, medians, and minimum, values as well as change from baseline by treatment group and study visit were similar between treatment groups. Maximum values of PTT were higher in the Heplisav-B group at Baseline and Weeks 8, 24, and 56. Maximum values for PT were higher in the Heplisav-B group at Weeks 24 and 56, in part due to subject 140-099 who received anticoagulation (see Section 6.3.12.2).

New-onset antiphospholipid antibodies of anti-cardiolipin IgG and IgM and anti-beta2 glycoprotein 1 IgG were uncommon and similar in both groups. For anti-beta2 glycoprotein 1 IgM, there were 19 subjects (9.2%) in the Heplisav-B group and two subjects (2.0%) in the Engerix-B group who had normal antibody levels at baseline and had at least one elevated level at Weeks 8, 24 or 56. Of subjects with Week 8 values and normal values at baseline, there were 16 subjects in the Heplisav-B group (8.3%) with elevated anti-beta2 glycoprotein 1 IgM levels at Week 8 (5 subjects > 40 units) compared to one subject in the Engerix-B group (1.1%, none > 40 units). One additional subject in the Heplisav-B group (140-060) had no baseline value, but a normal value at Day 10 and Week 4, and an elevated value at Week 8 (53 units). At other time points, the percentage of subjects with abnormal anti-beta2 glycoprotein 1 IgM was similar between groups.

Similar to the trend observed with anti-beta2 glycoprotein 1 IgM, there were more subjects in the Heplisav-B group with normal baseline lupus anticoagulant screen testing and elevated levels at Week 8 (n = 30, 19.9% of subjects with normal baseline levels), compared to Engerix-B (n = 5, 6.4% of subjects with normal baseline levels). This trend was not observed with the lupus anticoagulant confirmatory test. Nine subjects, all in the Heplisav-B group, were noted to have more than one antiphospholipid antibody test (all anti-beta2 glycoprotein 1 IgM and lupus anticoagulant screen) change from normal to elevated following vaccination.

Reviewer comment: *Antiphospholipid antibody testing is usually performed in the setting of a clinical suspicion for the syndrome, such as in a young patient with multiple*

thrombotic events or spontaneous abortions. Repeat testing is usually performed again at least 12 weeks later, as transiently elevated values can be detected following infection or drug exposure. While there are more subjects in the Heplisav-B group with new-onset elevated anti-beta2 glycoprotein 1 IgM and lupus anticoagulant screen at Week 8, the clinical significance of an abnormal test in the setting of no or low suspicion of antiphospholipid syndrome is uncertain. Please see Section 6.3.12.2 for a discussion of thrombophilia assessments in subjects who reported VTEs.

The mean chemistry and hematology values, standard deviations, medians, minimum and maximum values as well as change from baseline by treatment group and study visit were similar between treatment groups.

6.3.12.7 Dropouts and/or Discontinuations

Excluding fatalities, early discontinuation from study treatment due to a treatment-emergent MAE was reported in 0.5% Heplisav-B (30 subjects), 0.5% Engerix-B (14 subjects) recipients. Early discontinuation from study treatment due to an MAE assessed by the investigator as related was reported in seven subjects in the Heplisav-B group (0.1%) – 1) migraine, 2) diarrhea, 3) hypoesthesia and paresthesia on face with nausea, vomiting and diarrhea, 4) deep vein thrombosis (DVT), 5) Bell's palsy, 6) throat tightness and urticaria, and 7) hypersensitivity – and five subjects in the Engerix-B group (0.2%) – 1) arthralgia, migraine, and rash (potential AESI), 2) rash, 3) diarrhea, 4) DVT, and 5) nausea and vomiting. An additional adverse event (AE) of urticaria in subject 124-171 (see below) was reported two days following first injection with Heplisav-B, resulted in discontinuation of study treatment, and was assessed as unrelated.

In 125428/0.88, in response to an IR, the Applicant provided information on two subjects, noted above, in the Heplisav-B group who had events indicative of a possible allergic reaction beginning on the day of the first dose, assessed by the investigator as probably related, and leading to treatment discontinuation. A 51-year-old man (134-342) with a penicillin allergy reported itching at the injection site followed by generalized urticaria approximately 40 minutes after vaccination. Approximately 15 minutes later he reported difficulty swallowing and was treated, at the study site, with IV diphenhydramine and an oral steroid prescription. He was observed and released home. Urticaria was reported resolved the following day. A 46-year-old woman (136-022) reported nine days of "allergic reaction" (PT = Hypersensitivity, Grade 2) following injection, treated with epinephrine and diphenhydramine on Day 1 and IV methylprednisolone, IV diphenhydramine, IV famotidine, and oral prednisone on Day 3. The Applicant clarified the hypersensitivity was cervical lymphadenopathy beginning approximately two hours after vaccination. The subject self-treated with epinephrine and benadryl and when symptoms did not abate two days later, was treated with IV steroids in the emergency room.

Reviewer comment: *Rates of discontinuation from study treatment due to a treatment-emergent MAE were similar in treatment groups. Two events, one in each arm, were SAEs that led to treatment discontinuation, both DVTs. With regard to lymphadenopathy, in DV2-HBV-23, one additional subject in the Heplisav-B group, reported lymphadenopathy within one month of active vaccination (day 27), but in prior studies seven subjects who received Heplisav-B reported lymphadenopathy within one month of active vaccination, but only two of them were assessed as related. Subject 134-342 experienced an allergic, possibly anaphylactic, reaction following Heplisav-B. Based on the clinical review for the first review cycle, dated 24 February 2013, one*

subject was identified who withdrew (from study DV2-HBV-16) due to vaccine allergy. The Applicant has planned to assess anaphylaxis in their post-marketing pharmacovigilance study.

In 125428/0.63, in response to items in the September 2016 IR and November 2017 CR, the Applicant provided the following clarifications regarding several subjects withdrawn from the study:

- In response to item 15, the Applicant provided information for subject 124-171, a 35-year-old man with no history of allergies or allergic reactions, who reported hives on his lower extremities, spreading to the rest of his body, two days after the first dose of Heplisav-B. He reported no other symptoms. He was evaluated by his primary care provider who treated him with a Medrol dose pack and thought the event could be study vaccine related. The investigator assessed the event as unrelated given the event occurred two days following exposure, instead of immediately. Alternate causality was not assessed. The subject chose to discontinue treatment.
- In response to item 7, for the Applicant clarified that subject 115-124 who received Engerix-B was being evaluated for an AESI of dry mouth, which was being evaluated by the SEAC, and so the subject was discontinued prior to the third dose of study vaccine despite the final diagnosis of xerostomia (PT = dry mouth) being listed with a start date reflective of the much later date of final diagnosis.
- In response to item 18, the Applicant clarified that subject 126-079, who had a history of “elbow pain both” (PT = arthralgia), was withdrawn at the subject’s request for the MAE of “right knee, right wrist, right elbow soreness” (PT = arthralgia) beginning six days after Dose 1, which was assessed as not related to vaccine and treated with methylprednisolone and ibuprofen. The Applicant reports that no action was taken regarding study treatment for the subject’s other MAEs.
- In response to item 16, the Applicant clarified that several events were inadvertently omitted from the Applicant’s Table of study drug related MAEs leading to treatment discontinuation in the CSR. These events are described above.

Reviewer comment: *The Applicant’s responses were adequate and did not identify any additional safety concerns.*

6.3.13 Study Summary and Conclusions

Although study DV2-HBV-23 was designed primarily as a safety study, clinical immunogenicity was evaluated in all per protocol subjects as a secondary endpoint and in the subgroup of type 2 diabetics as a primary endpoint. A comparison of the peak SPR of Heplisav-B at Week 24 with the peak SPR of Engerix-B at Week 28 for all per protocol study subjects was performed. The timing of evaluation of the SPR for the Heplisav-B group differed in study DV2-HBV-23 (Week 24) from studies DV2-HBV-10 (Week 12) and -16 (Week 12) in that a later time point was used for evaluating Heplisav-B. Immunogenicity results for study DV2-HBV-23 indicated that the SPRs of both study groups were comparable numerically. Because the 95% CI of the difference in SPR between Engerix-B and Heplisav-B was greater than -10%, Heplisav-B was shown to be noninferior to Engerix-B. An evaluation of the SPR in the type 2 diabetic population and other subgroups of subjects, based on age, sex, race, BMI, and smoking status showed

that Heplisav-B was able to induce a strong immune response in all of these subject subgroups.

Results of study DV2-HBV-23 were consistent, numerically and statistically, with those seen in studies DV2-HBV-10 and -16. Non-inferiority between Heplisav-B and Engerix-B was shown for all PP subjects and for all subgroups, based on age, sex, race, and BMI.

In study DV2-HBV-23, the Safety Population consisted of 8368 subjects, 5587 who received at least one dose of Heplisav-B and 2781 who received at least one dose of Engerix-B. Subjects reported more baseline medical conditions than previous studies; but cardiac risk factors and baseline medical conditions indicative of increased cardiovascular risk were balanced between study groups.

Key safety endpoints of MAEs, SAEs, and AESIs were monitored through Week 56. Overall, the rate of all MAEs and SAEs reported in the 56-week study period were similar between the Heplisav-B and Engerix-B groups. An imbalance between treatment groups was noted in deaths. After excluding deaths that were due to overdose or injury, a small imbalance remains (0.29% Heplisav-B, 0.14% Engerix-B). A higher proportion of subjects in the Engerix-B group died due to non-injury, non-overdose deaths within three months of an active vaccination.

There was an imbalance between treatment groups noted in SAEs with the PT AMI, which persisted when PTs in the SMQ Narrow for MI were considered. Approximately three times as many subjects in the Heplisav-B group reported SAEs of MI, as identified by SMQ, compared to the Engerix-B group. There was no clear imbalance identified in CV risk factors between treatment groups at baseline. All subjects in both groups who reported SAEs of MI had one or more known risk factors for CV disease at baseline. The imbalance in MI in the Heplisav-B group is apparent at approximately two months after the second vaccination and persists through the remainder of the study. Imbalances in deaths and MIs in the Heplisav-B arm were not noted in the other trials submitted in support of the BLA. However, in general, in the other pivotal trials the enrolled study populations had notably lower prevalences of risk factors for CV disease.

The Applicant submitted a major adverse cardiovascular events (MACE) analysis, which included external expert blinded adjudication of events of cardiovascular death, MI, and stroke in the three pivotal studies. In DV2-HBV-23, adjudicated MIs were observed in 14 Heplisav-B recipients and 1 Engerix-B recipient (RR = 6.97, 95% Koopman score CI 1.17, 41.44). Numerical imbalances in stroke trended in the same direction. Events adjudicated as cardiovascular death were few. If deaths adjudicated as having an unknown cause are included, the imbalance trends in the same direction. The differences between the treatment groups is concerning given the magnitude of the difference, its observation in a randomized controlled trial, and the clinical significance of the event.

An imbalance was also noted in MAEs of herpes zoster, the clinical significance of which are unknown. No differences between study groups were noted in pulmonary embolism or other venous thromboembolic events.

A similar number of subjects in each treatment group reported potential AESIs that were referred to the Safety Evaluation and Adjudication Committee for evaluation. No new-onset vasculitic AESIs were identified during the 56-week study period. The SEAC did

not adjudicate any new-onset autoimmune event as related to vaccination. The SEAC adjudicated four subjects in the Heplisav-B group and no subjects in the Engerix-B group as having new-onset autoimmune events. The SEAC did not consider all events on the AESIs list to be autoimmune. The Applicant identified nine subjects in the Heplisav-B group (0.16%) and one subject in the Engerix-B group (0.04%) who reported a new-onset immune-mediated event, including the four events the SEAC determined to be autoimmune. One of these events was concurrent with and possibly caused by another condition (hypothyroidism and papillary thyroid carcinoma). While no events of GPA or THS were identified, an additional event of granulomatous dermatitis in the Heplisav-B group that appears to be new in onset was adjudicated by the SEAC as not autoimmune; the SEAC appears to question the diagnosis and evolution of the rash. The clinical reviewer considers this event an autoimmune skin disease with potentially concerning connections to the previously reported events of GPA and THS.

A laboratory sub-study was conducted in 309 subjects enrolled at two sites. Review of chemistry, hematology, and urinalysis assessments conducted at various time points through the 56-week study period did not identify any notable differences between study groups. While no imbalance in venous thromboembolic MAEs was observed, more subjects in the Heplisav-B group had normal baseline anti-beta2 glycoprotein 1 IgM levels and elevated Week 8 levels. No subjects with VTE had this abnormality. The significance of one abnormal antiphospholipid antibody level and its possible role, if any, in imbalances of events noted in this study is not known.

7. Integrated Overview of Efficacy

The study design and timing of the primary immunogenicity analysis differed between studies DV2-HBV-10, -16 and -23. Therefore, integration of the SPR data for the primary immunogenicity endpoint analysis in the Integrated Summary of Effectiveness is not appropriate.

7.1 Indication #1

Not applicable

7.1.8 Persistence of Efficacy

Persistence of efficacy was previously addressed in the original clinical review of this application. Please refer to the clinical review for BLA STN 125428/0 dated 26 February 2013.

8. Integrated Overview of Safety

In the March 2016 CR response, the Applicant submitted two integrated safety assessments on the primary safety population (PSP) and the total safety population (TSP). A summary of the studies used in these integrated assessments is provided in the table below.

Table 41. Studies included in the integrated safety analysis presented by the Applicant in the March 2016 complete response evaluating Heplisav-B and Heplisav-B constituents

Applicant's Integrated Population	Study # and Phase	Age (years)	Formulation of Heplisav-B	Heplisav-B Doses (mcg/mcg), Schedules, Number vaccinated	Comparator Schedules, Number vaccinated
PSP, TSP	DV2-HBV-23 Phase 3	18-70	Proposed	20/3000 Weeks 0, 4, N = 5587	Engerix-B Weeks 0, 4, 24, N = 2781
PSP, TSP	DV2-HBV-16 Phase 3	40-70	Proposed	20/3000 Weeks 0, 4, N = 1968	Engerix-B Weeks 0, 4, 24, N = 481
PSP, TSP	DV2-HBV-10 Phase 3	11-55	Proposed	20/3000 Weeks 0, 4, N = 1821, including 11 pediatric subjects	Engerix-B Weeks 0, 4, 24, N = 607, including 2 pediatric subjects
TSP	DV2-HBV-22 Phase 1	50-70	Proposed	20/3000 Weeks 0, 4, N = 25	None
TSP	DV2-HBV-14 Phase 2	11-55	Proposed	20/3000 Weeks 0, 4, N = 207	None
TSP	DV2-HBV0001 Phase 1	18-55	Previous	20/300, N = 8 20/650, N = 8 20/1000, N = 8 20/3000, N = 8 HBsAg alone 20 mcg, N = 8 1018 alone 300 mcg, N = 2 650 mcg, N = 2 1000 mcg, N = 2 3000 mcg, N = 2 All Weeks 0, 8	None
TSP	DV2-HBV-02 Phase 2	18-65	Previous	20/3000 One injection, N = 30	Engerix-B One injection, N = 29
TSP	DV2-HBV-03 Phase 2	18-28	Previous	20/3000 Weeks 0, 8, N = 48	Engerix-B Weeks 0, 8, 24, N = 51
TSP	DV2-HBV-04 Phase 2	40-70	Previous	20/3000 Weeks 0, 8, 24, N = 206	Engerix-B Weeks 0, 4, 24, N = 206
TSP	DV2-HBV-05 Phase 2	40-70	Previous	20/3000 Weeks 0, 8, 24, N = 48	Engerix-B Weeks 0, 4, 24, N = 47
TSP	DV2-HBV-08 Phase 2	18-39	Previous	20/3000 Weeks 0, 4 20/3000 Weeks 0, 8 10/1500 Weeks 0, 4 N = 61	None

Source: Adapted from BLA STN 125428/0.42, Summary of Clinical Safety, Table 2.7.4-1, p. 16-20.
N = number of subjects in the Safety population
PSP = Primary Safety Population
TSP = Total Safety Population

The Applicant included the three pivotal, Phase 3 trials in their PSP. Their TSP included all the studies in Table 41, including studies that utilized different doses, formulations, manufacturing and schedules of the vaccine. Subjects who received HBsAg alone (N = 8) or 1018 adjuvant alone (N = 8) were included in the Heplisav-B group in the integrated safety analysis.

An integrated safety analysis was conducted at the time of the original BLA submission. Safety information from two studies not included in the original BLA submission was included in the integrated safety analysis submitted in the March 2016 complete response, studies DV2-HBV-23 (reviewed in Section 6.3), and DV2-HBV-22, a phase 1 study of 25 subjects without a comparator vaccine.

8.1 Safety Assessment Methods
Please see Section 8.2.1 for a description of the length of time the Applicant monitored AEs, MAEs, SAEs, and AESIs in each of their studies. The Applicant does not provide a description of the methods of collection of these adverse events (for example subject diary) in their Summary of Clinical Safety. Please see Section 6.3.12.1 for a description of methods for DV2-HBV-23, and the initial clinical review for the methods used in DV2-HBV-10 and -16.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety
The table below presents the studies included in the Applicant's integrated safety populations and the length of time for which each safety outcome was monitored for each study.

Table 42. Length of time after the first dose for safety outcome monitoring in studies included in the integrated safety analysis presented by the Applicant in the March 2016 complete response

Applicant's Integrated Population	Study #	AEs	MAEs	SAEs	AESIs
PSP, TSP	DV2-HBV-23	None	56 weeks	56 weeks	56 weeks
PSP, TSP	DV2-HBV-16	28 weeks	None	52 weeks	52 weeks
PSP, TSP	DV2-HBV-10	28 weeks	None	28 weeks	None
TSP	DV2-HBV-22	12 weeks	None	56 weeks	56 weeks
TSP	DV2-HBV-14	28 weeks	None	28 weeks	None
TSP	DV2-HBV0001	62 weeks	None	62 weeks	None
TSP	DV2-DV2-HBV-02	28 weeks	None	60 weeks	None

Applicant's Integrated Population	Study #	AEs	MAEs	SAEs	AESIs
TSP	DV2-HBV-03	28 weeks	None	50 weeks	None
TSP	DV2-HBV-04	24 weeks	None	50 weeks	None
TSP	DV2-HBV-05	12 weeks	None	32 weeks	None

Source: Adapted from 125428/0.42, Summary of Clinical Safety, Table 2.7.4-1, p. 16-20.

DV2-HBV-23 and DV2-HBV-22, the two studies for which data was not previously submitted in the initial April 2012 BLA submission, did not include monitoring for solicited adverse events; DV2-HBV-23 did not include monitoring for unsolicited AEs for which subjects did not seek medical attention. DV2-HBV-23 was the only study of Heplisav-B which monitored MAEs. CBER generally does not consider it appropriate to pool the unsolicited AE information collected in studies other than DV2-HBV-23 and the MAE information collected in DV2-HBV-23 because they represent different types of events and had different monitoring periods. Therefore, solicited adverse events and an integrated analysis of AEs and MAEs are not performed in this review. Please see the clinical review, dated 26 February 2013, of the initial submission for an integrated summary of solicited adverse events and unsolicited adverse events reported following Heplisav-B. Please see Section 6.3.12.2 for a summary of MAEs reported in DV2-HBV-23. This integrated overview will focus on SAEs and AESIs.

CBER had other concerns with the populations for which the Applicant conducted the integrated safety analysis. Studies included in the Applicant's PSP monitored SAEs for varying lengths of time: 28 weeks following the first dose in DV2-HBV-10, 52 – 56 weeks in DV2-HBV-23 and DV2-HBV-16. Some studies included in the Applicant's TSP used a previous formulation (some using different antigen strains), dose, or schedule, of the vaccine and included subjects who received antigen only and adjuvant only. Due to these concerns, CBER's presentation of the integrated overview of safety for SAEs uses the following populations:

- Primary Safety Population (PSP)
  - Six-month PSP:
    DV2-HBV-10, DV2-HBV-16, DV2-HBV-23 (all pivotal trials)
    SAEs reported from vaccination through 6 months following the first dose (day 197 was chosen to include all SAEs reported in HBV-10)
  - One-year PSP:
    DV2-HBV-16, DV2-HBV-23 (pivotal trials monitoring SAEs for one year)
    SAEs reported from vaccination through study end (Week 52-56)
- Modified Total Safety Population (mTSP)
  DV2-HBV-10, DV2-HBV-14, DV2-HBV-16, DV2-HBV-22, DV2-HBV-23 (trials using the final formulation)
  SAEs reported from vaccination through six months following the first dose (day 197)

The mTSP is presented through six months because only three studies monitored SAEs for one year: studies DV2-HBV-23, DV2-HBV-16, and DV2-HBV-22. No subjects in DV2-HBV-22, a 25-person uncontrolled study, reported SAEs or AESIs. Therefore, a

one-year mTSP would be equivalent to the one-year PSP in terms of the number of these events and would only minimally change the total number of subjects. Because DV2-HBV-14 and DV2-HBV-22 were uncontrolled studies, the mTSP only added subjects to the Heplisav-B group. Also of note, study DV2-HBV-10 included 13 subjects (11 Heplisav-B, 2 Engerix-B) who were younger than 18 years of age. None of these subjects reported SAEs and they are not included in the analysis below. CBER asked the Applicant to present an analysis of safety based upon the populations described above in item 43 of the November 2016 CR letter. The Applicant responded in 125428/0.74 in the 8 February 2017 response to the CR.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations
Demographic characteristics were similar by treatment groups for each safety population. Across both treatment groups combined in each of the integrated safety populations, subjects were well-balanced by gender (female 49.9 – 50.9%), and predominantly white (73.4 – 77.6%), not Hispanic (91.5 – 92.6%). The predominant non-white racial groups were Black or African American (19.3 – 23.3%), followed by Asian (1.2 – 1.5%). Mean age was 49.0 – 51.2 years (SD 11.1 – 11.6, median 50 – 52 years). There were no notable imbalances in demographics by treatment groups.

The table below summarizes selected risk factors for cardiovascular disease at baseline in the three pivotal studies. The reviewer generated all analyses for study DV2-HBV-10 and hypertension, which were not submitted by the Applicant, and for hyperlipidemia, because the Applicant's analysis did not include dyslipidemia.

Table 43. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav-B (DV2-HBV-10, -14, and -22)

Condition or characteristic	DV2-HBV-23 Heplisav-B N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16 Heplisav-B N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-10* Heplisav-B N = 1810 n (%)	DV2-HBV-10* Engerix-B N = 605 n (%)
At least one baseline medical diagnosis of cardiac ischemia†	211 (3.8)	99 (3.6)	50 (2.5)	15 (3.1)	13 (0.7)	2 (0.3)
Type 2 Diabetes‡	762 (13.6)	381 (13.7)	158 (8.0)	33 (6.9)	41 (2.3)	11 (1.8)
Hypertension§	2021 (36.2)	978 (35.2)	579 (29.4)	143 (29.7)	194 (10.7)	57 (9.4)
Hyperlipidemia¶	1757 (31.4)	879 (31.6)	587 (29.8)	152 (31.6)	147 (8.1)	47 (7.8)
Smoking within 1 year	1843 (33.0)	909 (32.7)	431 (21.9)	118 (24.5)	654 (36.1)	224 (37.0)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)	863 (43.9)	205 (42.6)	463 (25.6)	167 (27.6)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86 and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of the integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N = number of subjects in each treatment group
n = number of subjects reporting medical history item or characteristic
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of integrated studies
† Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease
‡ Defined as, in DV2-HBV-23, subjects identified as diabetic in the Diabetes History case report form; in DV2-HBV-16 and -10, subjects with a medical history term of diabetes and taking a drug with a WHO Drug ATC2 code of "DRUGS USED IN DIABETES"; in DV2-HBV-14 and -22, subjects with a medical history term of diabetes

§ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
¶ Reviewer-generated from 125428/0.42, Module 5.3.5.3 dataset ADMH of integrated studies, defined as subjects with at least one medical history preferred term for Dyslipidemia standard MedDRA query narrow

DV2-HBV-23 enrolled higher proportions of subjects with risk factors for cardiovascular disease and baseline history of cardiac ischemia compared to the other pivotal trials. Within each of the three pivotal trials, the rates of subjects reporting a medical history of and risk factors for cardiovascular disease at baseline were similar between treatment groups.

8.2.3 Categorization of Adverse Events
The Applicant coded all verbatim terms for unsolicited AEs, including SAEs, using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 and the resulting system organ class (SOC) and preferred terms (PTs) were used for tabulation of incidence rates. When available, trends in SMQs and HLTs were evaluated to assess similar events together.

Reviewer comment: *MedDRA tends to "split" closely related events leading to greater specificity but less sensitivity. Consequently, SMQs and HLTs provide a "lumped" assessment of such events.*

8.3 Caveats Introduced by Pooling of Data across Studies/Clinical Trials
The following limitations of the integrated safety analysis are introduced by pooling data from several studies:

- Monitoring of SAEs for varying lengths of time
- Varying randomization ratios
- Varying methods of identification and evaluation of AESIs
- Study populations with different baseline characteristics and risk for cardiovascular disease.

Reviewer comment: *The clinical review of the original BLA included an integrated safety analysis of all studies evaluating all formulations of Heplisav-B. Upon review of the March 2016 CR response, which included study DV2-HBV-23 that monitored AEs differently than previous studies, pooling of all studies was reevaluated and determined not to be the most appropriate analysis. CBER's three-part integrated safety analysis addresses the limitation regarding varying monitoring times for SAEs as much as possible. Only studies evaluating the proposed formulation have been included in this integrated analysis to address limitations introduced by using other manufacturing processes.*

Furthermore, due to the varying randomization ratios (4:1 in DV2-HBV-16, 3:1 in DV2-HBV-10, and 2:1 in DV2-HBV-23) and the lower prevalence of cardiovascular risk factors in the study populations of studies DV2-HBV-10 and -16 compared to study DV2-HBV-23, pooling of the three pivotal trials, particularly to assess cardiovascular risk, results in adding disproportionate numbers of low-risk Heplisav-B recipients to the integrated safety population. For these reasons, the reviewer considers that pooling of the pivotal trials is not the most appropriate way to assess cardiovascular risk.

8.4 Safety Results

8.4.1 Deaths
In addition to the 32 deaths reported in DV2-HBV-23 (See Section 6.3.12.3), there were two deaths in DV2-HBV-16. One 45-year-old male Heplisav-B-recipient with no relevant past medical history died of pulmonary embolus (b) (6) days after the second study injection. One 64-year-old male Engerix-B recipient died secondary to a PT of cardiac failure (b) (6) days after the second dose. As per the clinical review of the initial BLA submission, this death occurred two days following a heart attack. All deaths were determined to be unrelated by the investigators.

Table 44. All deaths and deaths due to causes other than injury or illicit drug overdose, Integrated Safety Populations

	6-month PSP Heplisav-B N = 9365 n (%)	6-month PSP Engerix-B N = 3867 n (%)	1-year PSP Heplisav-B N = 7555 n (%)	1-year PSP Engerix-B N = 3262 n (%)	mTSP (6 months) Heplisav-B N = 9597 n (%)	mTSP (6 months) Engerix-B N = 3867 n (%)
Deaths	15 (0.16)	5 (0.13)	26 (0.34)	8 (0.25)	15 (0.16)	5 (0.13)
Deaths not due to overdose or injury	9 (0.10)	3 (0.08)	17 (0.23)	5 (0.15)	9 (0.09)	3 (0.08)

Source: BLA STN 125428/0.74, Module 2.7.4, Summary of Clinical Safety, Table 3, p. 12.PSP primary safety population
mTSP modified total safety population
N = number of subjects in each treatment group
n = number of subjects reporting event

The Applicant considers nine deaths in the Heplisav-B group and three deaths in the Engerix-B group in study DV2-HBV-23, due to overdose or injury (deaths with an SOC of injury, poisoning, or procedural complications and the death with a PT of hypoxic ischemic encephalopathy, which was due to illicit drug overdose). Excluding overdoses and injuries, the rates of death in Heplisav-B groups ranged from 0.09% to 0.23%, and in Engerix-B groups from 0.08% to 0.15%.

Reviewer comment: *As discussed in Section 6.3.12.3, the clinical reviewer agrees those 12 deaths were due to overdose or injury. Even after the exclusion of these deaths, the imbalance in deaths in the 1-year PSP persists, driven by the deaths in study DV2-HBV-23. The rate of death is similar between treatment groups in the six-month PSP and mTSP, though a small numerical imbalance persists. One explanation for a greater frequency of deaths being observed in study DV2-HBV-23 is a population with more medical problems enrolled in study DV2-HBV-23 compared to the previous studies.*

8.4.2 Nonfatal Serious Adverse Events
SAEs and non-fatal SAEs occurred at similar rates in the Heplisav-B and Engerix-B treatment groups in the integrated safety populations and are displayed in the table below. CBER analysis and the Applicant analysis presented in 125428/0.74 Clinical Summary of Safety differ slightly because the CBER included events that happened on study day 197 in the six-month PSP and mTSP, in order to include all of the SAEs reported in study DV2-HBV-10. Proportions do not differ significantly.

Table 45. CBER analysis of number and percentage of subjects with treatment-emergent serious adverse events by treatment group, Integrated Safety Populations

Event	6-month PSP Heplisav-B N = 9365 n (%)	6-month PSP Engerix-B N = 3867 n (%)	1-year PSP Heplisav-B N = 7555 n (%)	1-year PSP Engerix-B N = 3262 n (%)	mTSP (6 months) Heplisav-B N = 9597 n (%)	mTSP (6 months) Engerix-B N = 3867 n (%)
At least one SAE	271 (2.89)	114 (2.95)	421 (5.57)	171 (5.24)	273 (2.84)	114 (2.95)
At least one non-fatal SAE	260 (2.78)	109 (2.82)	400 (5.29)	164 (5.03)	262 (2.73)	109 (2.82)

Source: Reviewer-generated analyses from BLA STN 125428/0.42, Module 5.3.5.3, ADAE integrated dataset.
mo month
PSP: primary safety population
mTSP: modified total safety population
N = number of subjects in each treatment group
n = number of subjects reporting event
SAE serious adverse event

The mTSP was the most inclusive population evaluated by CBER in the integrated analysis and the one-year PSP included monitoring for the longest time period. The most common SAE PTs reported in the Heplisav-B group in the mTSP were: acute myocardial infarction, non-cardiac chest pain, pneumonia, osteoarthritis, cellulitis, asthma, cholecystitis, cerebrovascular accident, chronic obstructive pulmonary disease, and hypertension. The most common SAE PTs reported in the Heplisav-B group in the 1-year PSP were: acute myocardial infarction, pneumonia, osteoarthritis, non-cardiac chest pain, chronic obstructive pulmonary disease, coronary artery disease, atrial fibrillation, small intestinal obstruction, cellulitis, cerebrovascular accident, and asthma. These SAEs were balanced between groups or were reported more frequently in the Engerix-B group with the following exceptions: acute myocardial infarction (mTSP 6 month: Heplisav-B 0.08%, Engerix-B 0.03%; 1-year PSP: 0.21% Heplisav-B, 0.06% Engerix-B) and asthma (mTSP 6 month: Heplisav-B 0.06%, Engerix-B 0.05%; 1-year PSP: 0.09% Heplisav-B, 0.03% Engerix-B). The imbalance in asthma SAEs in the 1-year PSP is slightly greater than the imbalance noted in study DV2-HBV-23; however, there is no imbalance in asthma SAEs in the mTSP, which is based on all subjects receiving the proposed formulation reporting events within six months following vaccination. Please see the discussion of myocardial infarction and cerebrovascular accident in the MACE analysis below.

An analysis grouping SAE PTs by narrow SMQs was conducted by the reviewer. All events identified in this preliminary analysis with the highest RRs and confidence intervals that exclude or nearly exclude one are discussed elsewhere in this document (see Section 6.3.12). Of note, in the one-year PSP, prostate malignant tumors were reported more frequently in the Engerix-B group (7 subjects, 0.21%) compared to the Heplisav-B group (5 subjects, 0.07%). In the six-month PSP, gallstone-related disorders were reported more frequently in the Engerix-B group (4 subjects, 0.1%) compared to the Heplisav-B group (1 subject, 0.01%). The Applicant notes that the prostate malignant tumors are reported at similar frequencies as adjudicated events of MI, though in the opposite treatment groups (see MACE analysis below for MI frequencies).

Reviewer comment: *No new safety concerns were identified in the integrated analysis that had not been identified previously. The reviewer does not agree that the imbalances in the frequencies of prostate malignancies are comparable to the events of MI. As many risk factors for prostate cancer overlap with risk factors for cardiovascular*

disease, pooling of these studies introduces disproportionately more low risk subjects to the Heplisav-B group, as described in Section 8.3. Furthermore, unadjudicated events of prostate cancer are not comparable to adjudicated events of MI, as an adjudication of prostate malignancies may lead to the exclusion of some events.

Cardiac SAEs and Myocardial Infarction

The table below shows the SAEs with PTs in the SMQ narrow for MI and all SAEs in the cardiac disorders SOC in the integrated safety populations. The table includes fatal SAEs.

Table 46. Number and percentage of subjects with cardiac serious adverse events and events of myocardial infarction (MedDRA SMQ narrow) by treatment group, Integrated Safety Populations

Event	6-month PSP Heplisav-B N = 9365 n (%)	6-month PSP Engerix-B N = 3867 n (%)	1-year PSP Heplisav-B N = 7555 n (%)	1-year PSP Engerix-B N = 3262 n (%)	mTSP (6 months) Heplisav-B N = 9597 n (%)	mTSP (6 months) Engerix-B N = 3867 n (%)
At least one SAE in SOC CARDIAC DISORDERS	**29 (0.31)**	**16 (0.41)**	**58 (0.77)**	**19 (0.58)**	**29 (0.30)**	**16 (0.41)**
At least one SAE of myocardial infarct*	**12 (0.13)**	**2 (0.05)**	**21 (0.28)**	**4 (0.12)**	**12 (0.13)**	**2 (0.05)**
Acute coronary syndrome	1 (0.01)	0	1 (0.01)	0	1 (0.01)	0
Acute myocardial infarction	8 (0.09)	1 (0.03)	16 (0.21)	2 (0.06)	8 (0.08)	1 (0.03)
Angina unstable	1 (0.01)	1 (0.03)	1 (0.01)	1 (0.03)	1 (0.01)	1 (0.03)
Coronary artery occlusion	1 (0.01)	0	1 (0.01)	1 (0.03)	1 (0.01)	0
Myocardial infarction	1 (0.01)	1 (0.03)	2 (0.03)	1 (0.03)	1 (0.01)	1 (0.03)

Source: Adapted from BLA STN 125428/0.74, Module 2.7.4, Summary of Clinical Safety Addendum, Table 4 and 5, pp. 17 and 21.
PSP: primary safety population
mTSP: modified total safety population
N = number of subjects in each treatment group
n = number of subjects reporting event
* Defined as the MedDRA SMQ Narrow for myocardial infarct.

All cardiac SAEs were more frequent in the Engerix-B groups in the integrated safety populations over the first six months. All cardiac SAEs were slightly higher in the Heplisav-B group in the one year integrated safety population. An imbalance in myocardial infarction (by narrow SMQ) was observed in the integrated populations, driven by the events in study DV2-HBV-23. One subject in the Engerix-B group in study DV2-HBV-16 had two SAEs, unstable angina and AMI, which started on the same day, and are considered to be one event.

The datasets were searched to identify possible events of MI in non-pivotal studies. In studies which used a previous formulation of Heplisav-B, two additional subjects reported an SAE in the SMQ narrow for MI – one subject who received Heplisav-B in study DV2-HBV-05 and reported an acute myocardial infarction 121 days following last active injection (dose 3), and one subject who received Engerix-B in DV2-HBV-04 and reported unstable angina (verbatim term “suspected unstable angina”) 14 days after the last active injection (dose 3). Both studies were double-blind, randomized trials

conducted in Asia that enrolled adults 40 – 70 years of age, randomized 1:1 to receive an earlier formulation of Heplisav-B (different antigen strain, same dose of antigen and adjuvant) at Weeks 0, 8, and 24 or Engerix-B at Weeks 0, 4, and 24. In both studies, SAEs were collected through Week 50.

Reviewer comment: *The imbalance in MI is diminished in magnitude, but persists when studies are pooled*

The Applicant conducted further analysis of SAEs of MI and other cardiovascular events reported in the three pivotal trials, submitted in 125428.0.65. These analyses included a multivariate logistic regression analysis, a MACE analysis, comparison of observed to expected rates, and an assessment of the Bradford Hill criteria, which are presented here. Input from CBER's cardiology consultations will be included in the discussion below and is also summarized in Section 5.4.2. Please also see the full consults in Appendix B.

Multivariate Logistic Regression Analysis: The Applicant conducted a multivariate logistic regression analysis for the pivotal trials with MI events (by preferred terms in the SMQ narrow for MI) as the dependent variable, and age, sex, race, hypertension, BMI, diabetes mellitus, smoking, history of MI or stroke, and treatment group as the independent variables. This analysis indicated that hypertension (Odds Ratio [OR] = 3.78; 95% CI: 1.44, 9.91) and age (OR = 1.07 per one year increase; 95% CI: 1.02, 1.13) were statistically significant independent predictors of MI. Treatment group was not a significant independent predictor of events identified by the MI SMQ (OR = 2.21; 95% CI: 0.76, 6.45). No other known risk factors for cardiovascular disease were found to be significant independent predictors in this model.

Reviewer comment: *The OR, while not significant, is greater than 1. While, this is a reasonable analysis to conduct, the model has limitations. In addition to the issues previously noted regarding pooling of these trials, limitations include a small number of MI events leading to limited power to draw robust conclusions. This is evidenced by other known risk factors for CV disease also not demonstrating statistical significance. Other potential limitations of this model, as suggested by CBER consultations, include no distinction between first and recurrent events, omission of some covariates (for example dyslipidemia), and use of binary variables instead of continuous variables.*

Major Adverse Cardiovascular Events Analysis: In order to further assess the cardiovascular events that were reported in the pivotal trials, the Applicant conducted a major adverse cardiovascular events (MACE) analysis. Please see the description of the methods used for this analysis in Section 6.3.12.4. The results of the subjects identified as reporting an adjudicated MACE outcome in the three pivotal trials are presented in the table below. The table presented here differs from that presented by the Applicant. It does not include study DV2-HBV-10 as no MACEs were identified in that study and it does not display the pooled pivotal studies based on the reasons why pooling is not appropriate stated above. The table here also includes 95% Koopman confidence intervals, which CBER statisticians consider more appropriate for evaluating the MACE outcomes in these studies.

Table 47. Applicant-identified, adjudicated, treatment-emergent, serious three-point major adverse cardiovascular events by treatment group, DV2-HBV-23 and DV2-HBV-16, Safety Populations

Adjudicated MACE Outcome	DV2-HBV-23 Heplisav-B N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-23 Relative Risk (95% CI)[a] (95% CI)[b]	DV2-HBV-16 Heplisav-B N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-16 Relative Risk (95% CI)[a] 5% CI)[b]
Composite 3-point MACE events	28 (0.50)	6 (0.22)	2.32 (0.96, 5.60) (0.99, 5.46)	3 (0.15)	2 (0.42)	0.37 (0.06, 2.19) (0.07, 1.83)
Cardiovascular death*	3 (0.05)	1 (0.04)	1.49 (0.16, 14.35) (0.21, 10.42)	1 (0.05)	1 (0.21)	0.24 (0.02, 3.9) (0.01, 4.09)
Myocardial infarction†	14 (0.25)	1 (0.04)	6.97 (0.92, 52.97) (1.17, 41.44)	2 (0.10)	1 (0.21)	0.49 (0.04, 5.38) (0.06, 3.73)
Stroke‡	11 (0.20)	4 (0.14)	1.37 (0.44, 4.30) (0.46, 4.07)	0	0	-

Source: Adapted from 125428/0.65, Module 2.7.4, Evaluation of acute myocardial infarction and major adverse cardiovascular events in the Phase 3 Heplisav-B clinical trials, Table 3-3, p. 16
N = number of subjects in each treatment group
n = number of subjects reporting adverse event
CI: confidence interval
MACE major adverse cardiovascular events
a Wald confidence interval (Dynavax analysis)
b Koopman score confidence interval (CBER analysis)
* Cardiovascular cause of death comprises the following preferred terms: Death from cardiovascular cause includes death due to Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.
† Myocardial infarction includes deaths due to myocardial infarction and comprises the following preferred terms: Myocardial infarction includes Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, or Silent Myocardial Infarction.
‡ ‡ Stroke includes deaths due to stroke and comprises the following preferred terms: Stroke includes Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Hemorrhagic Stroke, Hemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischemic Cerebral infarction, Ischemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke.

The reviewer identified two subjects who are likely not appropriately represented in the table above. One subject who received Engerix-B in DV2-HBV-16 experienced a fatal MI (see Section 8.4.1). The PT was listed as "heart failure" and the event was not identified for review for adjudication of MI based on the selected PTs. However, the event was adjudicated as a cardiovascular death. In the opinion of the reviewer, this subject also experienced an MI based upon the narrative. Classification as an MI would not change the three-point MACE outcome for study DV2-HBV-16. However, as the Clinical Events Committee [MACE analysis] Charter allows adjudicators to identify additional events for adjudication, it is possible the adjudicators did not think there was enough evidence of MI and did not refer it for MI adjudication. The reviewer identified one subject (131-109) in the Heplisav-B group in study DV2-HBV-23 who experienced a stroke, confirmed by MRI, reported with a PT of transient ischemic attack and, thus, not reviewed for adjudication. If these subjects are accounted for in the table above, in study DV2-HBV-16, two Engerix-B subjects reported MI (0.42%, RR = 0.24, 95% Koopman score CI 0.04, 1.38) and the three-point MACE outcome remains the same. In study DV2-HBV-23, 12 subjects reported stroke (0.21%, RR = 1.49, 95% Koopman score CI 0.51,4.39) and 29 Heplisav-B recipients experienced a three-point MACE outcome (0.52%, RR = 2.41, 95% Koopman score CI 1.03, 5.64).

Reviewer comment: *Events in the table do not include events that were adjudicated as not having enough information to make a determination (see Section 6.3.12.3). If a worse case scenario is applied and the seven events adjudicated as "an unknown cause of death' are included as CV deaths, accounting for the reviewer-identified event of stroke noted above, 10 subjects in the Heplisav-B in DV2-HBV-23 would be categorized as having a cardiovascular death (0.18%, RR = 4.98, 95% Koopman score CI , 0.82, 30.16) and 36 subjects in the Heplisav-B group would have experienced a three-point MACE outcome (0.64%, RR = 2.99, 95% Koopman score CI (1.29, 6.91).*

In study DV2-HBV-23, the risk of three-point MACE outcomes was greater in the Heplisav-B arm compared to the Engerix-B arm. There were few adjudicated CV deaths. There was an imbalance in adjudicated events of MI, such that subjects in the Heplisav-B arm had 6.97 times greater risk of MI than subjects in the Engerix-B arm. Events of adjudicated stroke also trended toward a greater risk in the Heplisav-B arm. There were few adjudicated MACEs in study DV2-HBV-16 and none in study DV2-HBV-10.

Reviewer comment: *Blinded adjudication of selected cardiovascular events shows increased risk of MI compared to Engerix-B in study DV2-HBV-23. This risk was not observed in studies DV2-HBV-10 and -16. However, study DV2-HBV-23 enrolled a study population enriched with subjects with diabetes and other risk factors for cardiovascular disease. It is possible that a real and increased risk would not be identified until studies were conducted in a population with a greater underlying risk of the event.*

Observed vs. Expected MACEs: The Applicant compared the rates and numbers of adjudicated MACE events observed in the three Phase 3 trials to expected rates obtained by age, sex, and race adjusted estimates from population-based data and to expected rates obtained by risk prediction models that account for cardiovascular risk factors in the study populations. The Applicant concludes that the observed number of major cardiovascular events in Heplisav-B recipients is similar to or lower than expected and that the observed number of major cardiovascular events in Engerix-B recipients is

lower than expected. Thus, they conclude the imbalance in MACEs is due to a lower than expected number of events in the Engerix-B group as opposed to an excess of events in the Heplisav-B group.

Reviewer comment: *The imbalance noted in study DV2-HBV-23 was observed in a randomized controlled trial with a study population that may not be directly comparable to the general population upon which estimates were based. Furthermore, lack of prospective collection of cardiovascular events may have led to under-ascertainment of events. Lack of testing for certain risk factors, such as cholesterol in DV2-HBV-23 also limits interpretation of the data, although the Applicant assumed optimal cholesterol levels, providing a conservative estimate of expected MI events. In the opinion of the reviewer, the most appropriate comparison is to the control group within the study.*

The Applicant also presented an analysis of causality based upon seven Bradford Hill criteria, which is summarized here:

- Temporality: The Applicant notes a lack of temporal association and lack of imbalance through 42 days after the second dose.

  Reviewer comment: *While an increased risk of MACE was not observed in the 42-day window following Heplisav-B administration, there does appear to be an excess of events in the Heplisav-B arm beginning approximately 3 months following the first vaccination, two months following the second. The Applicant's reasoning also does not account for mechanisms that may accelerate disease and increase risk over time. Furthermore, immunogenicity data show that the SPR following Heplisav-B continued to increase between month 3 (one month after dose 2) and month 6 (five months after dose 2) (see review of immunogenicity for studies DV2-HBV-10 and -16 under BLA STN 125428/0, dated 26 February 2013). Based on this it appears that there are ongoing immunologic effects several months after vaccination, that could explain and provide evidence to support the vaccine's potentially prolonged effects on safety.*

- Strength/Effect Size: Across all MACE comparisons, relative risks (RR) ranged from 0.24 in DV2-HBV-16 to 6.97 in DV2-HBV-23 (with RR for cardiovascular death 1.49 and RR for stroke 1.37). None reached statistical significance.

  Reviewer comment: *To establish the safety of an antidiabetic drug to treat type 2 diabetes prior to a submission for licensure, CDER recommends demonstrating the upper bound of the two-sided 95% CI for the estimated risk ratio is less than 1.8. The relative risk of MI and the three-point composite MACE outcome in study DV2-HBV-23 is higher than 1.8.*[51] *Statistical significance based upon the 95% Wald CI is not the most appropriate method of assessing the statistical significance of these imbalances, as per CBER statisticians. Furthermore, statistical significance does not equate to clinical significance. In particular, the assessment of a potential safety signal in a study that was not powered or designed to prospectively assess this outcome should not rely on demonstration of statistical significance.*

- Consistency: The Applicant notes that this imbalance was not observed with other Heplisav-B trials.

Reviewer comment: *The prevalence of cardiovascular risk factors was greater in Study DV2-HBV-23 than in other studies of Heplisav-B.*

- Coherence: The Applicant notes that across studies, the magnitude and direction of each MACE outcome varies.

  Reviewer comment: *While this observation is true, the small number of events in prior studies limits the ability to draw firm conclusions.*

- Specificity/Alternate explanations: All subjects with MI were at high baseline risk of such events.

  Reviewer comment: *The Applicant's observation is true and it is possible the differences in cardiovascular events happened by chance. However, study DV2-HBV-23 was randomized and baseline characteristics between treatment groups were similar. The clinical reviewer notes no clear explanation for the why the magnitude of the risk was greater in the Heplisav-B group compared to the Engerix-B group.*

- Biologic Plausibility: The Applicant notes the following underlying causes of acute MI and their reasoning for why this association is not supported by biologic plausibility:
  - Rupture or destabilization of atherosclerotic plaque as may be caused by an acute inflammatory response to infection: systemic levels of the 1018 adjuvant following Heplisav-B are below those needed to activate pDCs in plaque, it is not known whether TLR9 stimulation would trigger plaque rupture, and the temporal association seen in study DV2-HBV-23 is not consistent with the short time interval that one is at increased risk of an acute coronary event following acute infection.
  - Acute vessel thrombosis: there is no evidence for hypercoaguability following Heplisav-B based on the reported frequency of venous thromboembolic events in the pivotal trials being similar between treatment groups. In addition, the laboratory sub-study demonstrated a transient rise in anti-beta2 glycoprotein 1 IgM in more subjects in the Heplisav-B group compared to the Engerix-B group, but no subjects with elevations reported thrombotic events.
  - Myocardial oxygen supply demand mismatch: There was no evidence of a change in heart rate and blood pressure at the time points at which it was measured during the study.
  - Atherosclerosis: The dose and route of administration of the 1018 adjuvant in Heplisav-B is not consistent with stimulation of a chronic inflammatory state that appears to be required for progressive atherosclerosis and there is no evidence of increased atherosclerotic events, other than MI, in the Heplisav-B groups in the three pivotal trials.

  Reviewer comment: *A definite biologically plausible mechanism is not known, nor does it need to be known in order for an agent to cause or contribute to an outcome.*

- Analogy: Influenza vaccines are associated with a reduction in the incidence of MACE events, yellow fever vaccine and herpes zoster infection stimulate TLR9 and neither yellow fever vaccine nor Zostavax are associated with cardiovascular events.

  Reviewer comment: *The clinical reviewer agrees that there are no established safety signals of cardiovascular events in the above licensed vaccines.*

The Applicant concludes that none of the criteria support causality.

Reviewer comment: While an evaluation using the Bradford-Hill criteria are reasonable to explore causality, particularly in observational studies, differences noted in DV2-HBV-23 between study groups were observed in a randomized, controlled trial. Therefore, the within study differences between treatment groups are more relevant than the differences noted between the observed rates and those that may be expected based on a population external to the study.

8.4.3 Study Dropouts/Discontinuations
The Applicant provided an analysis of subjects who discontinued from study treatment following an AE. These numbers were small and similar between study groups.

8.4.4 Common Adverse Events
Adverse events that were not medically attended are not evaluated in this submission because they were not monitored in Study DV2-HBV-23. Please see the clinical review of the original BLA.

8.4.5 Clinical Test Results
The Applicant does not provide an integrated analysis of clinical laboratory test results that includes results from studies DV2-HBV-23 or DV2-HBV-22. In their Clinical Summary of Safety submitted in 125428/0.42, the Applicant describes the results of testing for renal function and thrombotic disease on a subset of subjects in study DV2-HBV-23, and testing of chemistry and hematology in study DV2-HBV-16, separately. They also include a presentation of testing for autoantibodies conducted in studies included in the initial BLA submission. Review of the clinical laboratory testing from study DV2-HBV-16 and autoantibody testing was included in the clinical review of the initial BLA. Results of the laboratory sub-study in study DV2-HBV-23 are discussed in Section 6.3.12.6.

8.4.6 Systemic Adverse Events
Solicited adverse events, including systemic solicited AEs, were not evaluated in this review because they were not monitored in study DV2-HBV-23. Please see the clinical review of the original BLA for discussion of solicited events. The 22 February 2013 CR letter (item 2) requested additional information regarding subjects with events that may be considered unsolicited systemic adverse events or AESIs. The Applicant's responses, submitted in STN 125428/0.34 and 0.35 regarding subjects with non-AESI unsolicited adverse events are reviewed here and responses regarding AESIs are reviewed in Section 8.4.8.

In the BLA review dated 26 February 2013, five Heplisav-B subjects were identified that reported PE; the CR letter requested clotting disorder evaluations and any serologic markers of autoimmune disease on three of these subjects. The Applicant submitted

additional information for these subjects in STN 125428/0.34 (subjects 21-047, 22-070, 22-602) and 125428/0.35 (subject 22-070).

Subject 21-047 (study DV2-HBV-10) was a 32-year-old woman with a medical history that included obesity, smoking, and use of an etonogestrel ethinyl vaginal ring. She reported pain in her right arm 38 days after her second study injection. The pain worsened and she was admitted and was diagnosed with pulmonary embolism, pleuritis, pneumonia and cystitis 44 days following her second study injection. The narrative of the event states that "a thrombophilia diagnostic study was negative, but antiphospholipid antibodies were elevated." An ultrasound examination of the legs was limited due to the subject's obesity but no sign of deep vein thrombosis was found on this limited exam. The investigator assessed the event as severe and probably not related to study treatment. Anti-dsDNA and ANA testing at baseline and study conclusion were negative. In 125428/0.34, the Applicant submitted results of ANCA testing of study samples, which were all negative, CRP testing of study samples (1.88 – 3.06 mg/dL, no normal range provided), and results of hospital laboratory tests. Hospital laboratory testing at admit showed an elevated CRP (11.2 mg/dL, normal range 0 – 0.5), normal INR and PTT, elevated fibrinogen (>600 mg/dL, normal 180 - 350), and elevated d-dimer (0.8%, 0 – 0.3). Results of antiphospholipid antibodies were not included.

Subject 22-070 (study DV2-HBV-10) was a 26-year-old male with a medical history of asthma, who had a traumatic rupture of the anterior cruciate ligament of the right knee one month after his second study injection. He was treated with prophylactic dalteparin, but developed phlebothrombosis of the complete right leg and subsequent pulmonary embolism. He was discontinued from the study due to this SAE. The investigator assessed the event as severe in intensity and not related to study treatment. At the time of study discontinuation, an evaluation of hereditary causes of thrombosis was pending. Anti-dsDNA and ANA testing at baseline and study conclusion were negative. In response to CBER's request, the Applicant submitted results of ANCA and CRP testing of study samples (all normal), hospital records including laboratory results, and follow-up information on subject status. As per the subject's discharge summary, "thrombophilia was diagnosed on an outpatient basis prior to the initiation of therapy with Marcumar. A test for lupus inhibiting bodies was positive; this may be a temporary phenomenon. We believe that the increased Factor VIII activity is most likely related to a reactive elevation." Tests for hereditary thrombophilias were negative. Follow-up evaluation of the abnormalities was recommended in two months; these results were not provided. However, in a follow-up contact with the subject, he reported that an initial work-up for the etiology of pulmonary embolism had been negative and following discontinuation of anticoagulation, he had another left leg DVT six months after the first event in the setting of right knee surgery and despite prophylaxis. As per the subject's report, another workup at that time did not determine the etiology. Lifelong anticoagulation therapy was recommended.

Subject 22-602 (study DV2-HBV-16) was a 62-year-old male with a past medical history that included hyperlipidemia, hypertension, obesity, sleep apnea treated with continuous positive airway pressure and hand tendonitis, who was admitted eight months after the last active study injection with extensive bilateral pulmonary emboli. He had a clot at the bifurcation of the main pulmonary arteries and an extensive clot extending into the upper and lower lobes of both lungs. Ultrasound evaluation showed an extensive deep venous thrombosis of the left leg in the main femoral vein, popliteal, posterior tibial and peroneal veins. An evaluation for an underlying clotting disorder was planned and results were

pending at the time of the initial review. He had a history of frequent travel and had recently taken an interstate road trip. The investigator assessed the events as severe and not related to study treatment. Anti-dsDNA and ANA testing at baseline and study conclusion were negative. The Applicant submitted records from the PCP approximately two years later. The laboratory results performed while the subject was on anticoagulation indicate the subject has a factor V Leiden mutation, Protein C and Protein S deficiency, and prothrombin variant. The PCP note also indicates the subject had a history of factor V Leiden, discontinued anticoagulation for a dental procedure, and went on a car trip, resulting in a DVT and PE. It is not entirely clear if this refers to the event on-study, though it seems to describe it. Of note, this subject is incorrectly identified as 22-601 in the previous clinical review and the CR letter.

Reviewer comment: *Subject 22-602 has clear hereditary and circumstantial risk factors for thrombophilia and the event is more likely due to these factors than vaccine. Subjects 21-047 and 22-070 clearly had clinical risk factors for thrombophilia. However, they also both reported VTE events approximately one month following the second dose of Heplisav-B, with reports of positive antiphospholipid antibodies. This is at approximately the same time that a small increase in subjects in the laboratory sub-study of DV2-HBV-23 had increases in some anti-phospholipid antibodies. The clinical reviewer can't definitively determine that the vaccine did not contribute to these two events. However, in DV2-HBV-23, there was no overlap observed between subjects with abnormal* anti-beta 2 glycoprotein or anti-cardiolipin *antibodies and VTE events.*

Hospital records and neurological outpatient follow-up information for subject 06-174 (study DV2-HBV-10), a Heplisav-B recipient, were requested by CBER because of an unclear diagnosis of an SAE that included multiple neurologic complaints. In 125428/0.34, the Applicant submitted records from hospitalization and outpatient follow-up. The exact diagnosis is still unclear. The subject was admitted with facial numbness, dysphasia, and unilateral hand numbness approximately three months following dose 2. A stroke was suspected, but head CT and MRI were normal. The hand numbness was suspected to be secondary to carpal tunnel syndrome. On outpatient follow-up, the neurologist noted that he had "no symptoms suggestive of recurrent cerebral ischemia" and that "it is somewhat surprising that his MRI was completely normal."

Reviewer comment: *Based upon the evaluations of the treating physician, an SAE of resolved cerebral ischemia, as the event appears in the integrated ADAE, appears to be a reasonable way to report the event.*

Medical records regarding evaluation of a rash and facial swelling in subject 42-320 (study DV2-HBV-16) were requested by CBER. Study progress notes were submitted as the subject declined to release records. The following summary is from the previous clinical review, the additional progress notes, and information in the datasets. The subject was a 57-year-old female Heplisav-B recipient with a medical history that included osteoarthritis, pain in legs and feet and allergic rhinitis, who developed a rash on her stomach of unknown cause on the day of the first study injection, which resolved within hours. The investigator assessed the event as mild in intensity and possibly related to the study treatment. She received her second vaccination as scheduled. At approximately the same time she began tramadol, amitriptyline and naproxen for bilateral hand and foot pain, which is reported as pre-existing. Six weeks after her second injection, she developed swelling of the face of unknown cause for which she received diphenhydramine and an eight-day course of oral prednisone. Nine days after

the facial swelling, she developed a “skin rash” of unknown cause. Further vaccinations were not administered due to the unknown nature of the rash. The investigator assessed the events of rash (following dose 2) and facial swelling as mild in intensity and unrelated to the study treatment. The additional progress notes reviewed revealed that the subject was evaluated by a dermatologist. As per the subject the rash did not recur following tramadol discontinuation. However, it is noted that the first rash was reported prior to tramadol use and, as no other cause is known; the first rash is assessed as possibly related to vaccine. No further information is provided regarding the facial swelling, with the possible exception of one note that says “Subject confirms no history of swelling or itching since 2010 incident.” The Applicant also reports the subject had negative anti-ds DNA titers at baseline and at the end of study, but ANA <1:40 at baseline and 1:40 with a nucleolar pattern at Week 52.

Reviewer comment: *Though information is limited, events appear to be recorded adequately. In the opinion of the clinical reviewer, it is unlikely that one event of facial swelling six weeks following the last vaccination is related to an allergic reaction to Heplisav-B, but an autoimmune disease was not ruled out. The etiology of the swelling and rash is unknown.*

8.4.7 Local Reactogenicity

Not evaluated in this submission. Please see the clinical review of the initial BLA submission.

8.4.8 Adverse Events of Special Interest

AESIs were collected prospectively in pivotal studies DV2-HBV-16 and -23 and in supportive study DV2-HBV-22. In these studies, AESIs were pre-specified by a list and potential AESIs identified by the investigators were referred to a specialist and to the SEAC (if confirmed to be autoimmune in DV2-HBV-16) for evaluation. In their Clinical Summary of Safety, the Applicant identified AESIs retrospectively by PT search for terms on the AESI list and excluded events with verbatim terms that indicated worsening of a pre-existing condition. The Applicant presented AESIs in all studies together, regardless of the method of monitoring and identifying AESIs.

Reviewer comment: *Studies that did not prospectively define and monitor AESIs and did not use a SEAC to adjudicate cases, lack the safety data collection rigor that studies that prospectively defined and collected AESIs and used a SEAC to adjudicate cases did. Therefore, in the opinion of this clinical reviewer, these studies with different safety monitoring procedures should not be pooled. While the reviewer considered all studies submitted to the BLA, including studies that used a prior formulation, to identify AESIs, the reviewer presents AESIs identified in studies that used a SEAC and studies that did not use a SEAC separately. Because the Applicant identifies AESIs in their Clinical Summary of Safety in 125428/0.42 by PT search, some events that were referred to the SEAC, potentially adjudicated as autoimmune or AESIs, but for which the preferred term did not reflect the final diagnosis, are not included in their analysis (for example, hypothyroidism, instead of Hashimoto’s thyroiditis). The applicant corrected this in their Clinical Summary of Safety addendum submitted in 125/428/0.74. However, in the addendum, they do not include two events reported in study DV2-HBV-23 (VIth nerve palsy, and diplopia/IIIrd nerve palsy), which are AESIs. The reviewer agrees it is reasonable not to categorize them as immune-mediated, given the identified reasonable alternative plausible cause of diabetes.*

Please see Section 6.3.12.5, where AESIs identified in study DV2-HBV-23 are described in detail. Briefly, the following events were reported in study DV2-HBV-23 in the Heplisav-B group and were assessed by the SEAC or Applicant as immune-mediated: Bell's palsy (n = 5), alopecia areata, polymyalgia rheumatica, ulcerative colitis, and hypothyroidism. The event of hypothyroidism attributed to papillary thyroid cancer. One Engerix-B subject reported Bell's palsy. In addition, this analysis does not include a subject who received Heplisav-B, was diagnosed with granulomatous dermatitis, and did not receive an evaluation for sarcoidosis as was recommended by treating physicians. No events were determined to be related by the SEAC.

Please see the clinical review of the initial BLA for a full discussion of the AESIs that were identified prospectively in study DV2-HBV-16 and retrospectively in the initial integrated safety summary. Briefly, the SEAC in DV2-HBV-16 adjudicated the following events as new-onset autoimmune events in subjects who received Heplisav-B: hypothyroidism (n = 2), vitiligo (n = 1). The event of vitiligo occurred in a subject with pre-existing psoriasis. An event of Tolosa-Hunt syndrome (THS) in the Heplisav-B arm was not reviewed by the SEAC at the time of the study, but is now considered by the Applicant to be a new-onset autoimmune adverse event (see Section 5.4). Two events in the Heplisav-B arm were adjudicated by the SEAC as not autoimmune, but are new-onset immune-mediated (AESIs) events: Bell's palsy (n = 1), and erythema nodosum (n = 1). The event of erythema nodosum was determined by the SEAC to be related. No other events were assessed by the SEAC as related. There were no events adjudicated as autoimmune or immune-mediated in the Engerix-B arm. In 125428/0.42, the Applicant also identified an additional event of dermatitis herpertiformis in a subject who received Heplisav-B in study DV2-HBV-16, that was not identified as an AESI during the trial or in the BLA submission. However, in a follow-up communication, the subject and her primary care physician denied that the subject was ever diagnosed with the condition.

There were no AESIs identified in study DV2-HBV-22.

In summary, in studies that pre-specified monitoring for AESIs and used a SEAC to assess AESIs, there were 15 new-onset immune-mediated adverse events (0.2%) in the Heplisav-B arm and 1 in the Engerix-B arm (0.03%), as determined by the Applicant (Table 48). This does not include the event of granulomatous dermatitis that the reviewer considers immune-mediated and to have potential connections to the two other events of granulomatous disease following Heplisav-B.

Table 48. Applicant- or SEAC-categorized new-onset immune-mediated adverse events in studies which prospectively monitored for such events (DV2-HBV-16, -22, and -23)

Treatment Arm	Study	Age Sex	Adverse event	Last Active Dose	Days After Last Active Dose	AI per SEAC	Background incidence per year
Heplisav-B	DV2-HBV-23	52 F	Alopecia areata	2	229	Yes	8.8-29.3 per 100,000[44]
Heplisav-B	DV2-HBV-23	46 F	Ulcerative colitis	2	221	Yes	2.2-14.3 per 100,000[39]
Heplisav-B	DV2-HBV-23	68 M	Polymyalgia rheumatica	2	292	Yes	52.5 per 100,000 (adults 50 years and older)[40, 41, 42]
Heplisav-B	DV2-HBV-23	60 F	Hypothyroidism*	2	246	Yes	350 per 100,000 women[38§]
Heplisav-B	DV2-HBV-23	49 M	Bell's Palsy	1	10	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-23	52 M	Bell's Palsy	2	256	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-23	31 F	Bell's Palsy	2	169	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-23	49 F	Bell's Palsy	2	1	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-23	49 M	Bell's Palsy	1	172	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-16	68 M	Tolosa-Hunt syndrome	2	292	Yes	1 per 1,000,000[1]
Heplisav-B	DV2-HBV-16	58 F	Hypothyroidism	1	27	Yes	350 per 100,000 women[38§]
Heplisav-B	DV2-HBV-16	52 F	Hypothyroidism	2	30	Yes	350 per 100,000 women[38§]
Heplisav-B	DV2-HBV-16	62 M	Erythema Nodosum[†]	2	20	No	1-5 per 100,000[52]
Heplisav-B	DV2-HBV-16	59 M	Bell's Palsy	2	271	No	13-34 per 100,000[43]
Heplisav-B	DV2-HBV-16	69 M	Vitiligo[‡]	2	2	Yes	0.1 – 2.0 per 100[53¶]
Engerix-B	DV2-HBV-23	29 M	Bell's Palsy	3	27	No	13-34 per 100,000[43]

AI = autoimmune
SEAC = Safety Evaluation and Adjudication Committee
* The event of hypothyroidism (Hashimoto's thyroiditis) was assessed as l kely due to papillary thyroid carcinoma diagnosed following this event.
† SEAC assessed as related to vaccine.
‡ Subject had a pre-existing autoimmune condition of psoriasis prior to study enrollment.
§ Incidence of overt spontaneous hypothyroidism due to any cause
¶ Numbers presented are prevalence; incidence not available.

Reviewer comment: *There is an imbalance in immune-mediated events, with more events being reported in the Heplisav-B group. The overall incidence of immune-mediated disorders was low. However, limitations of sample size and safety follow-up periods, the relatively low background incidence of autoimmune events, and the indolent nature of many of these diseases make accurate assessment of risk of immune-mediated disease with Heplisav-B difficult. However, two pivotal studies utilizing a blinded panel have both shown an imbalance in AESIs, with the Heplisav-B group reporting approximately 6.5 times as many immune-mediated events as the Engerix-B group.*

In studies that did not pre-specify AESIs and utilize a SEAC, including studies that did not use the final formulation, the Applicant retrospectively searched the safety database for PTs from the list of AESIs used in the studies that prospectively monitored AESIs. Six subjects in the Heplisav-B groups (0.2%) reported AESIs: granulomatosis with polyangiitis, Guillain-Barré syndrome, Grave's disease, lichen planus, Bell's palsy, and uveitis. Five subjects in the Engerix-B groups (0.5%) reported AESIs: p-ANCA-positive vasculitis in a subject with pre-existing mixed connective tissue disease, Bell's palsy, Grave's disease, Raynaud phenomenon, rheumatoid arthritis. Of note, the clinical review (dated 26 February 2017) of the initial BLA submission did not identify the subject with lichen planus and included three subjects that are now excluded from the above summary. These subjects are two Heplisav-B recipients in DV2-HBV-10 with worsening disease (one with rheumatoid arthritis and one with systemic lupus erythematosus) and one Heplisav-B recipient in DV2-HBV-0001 with rheumatoid arthritis diagnosed on study day 556.

Reviewer comment: *The lack of prospective monitoring and of adjudication of events makes a comparison of the rates of AESIs between study groups unreliable and makes comparison of these rates with SEAC-adjudicated rates uninformative. Furthermore, subjects in DV2-HBV-10, the pivotal and largest trial that did not utilize a SEAC, were only monitored for 28 weeks following first vaccination and immune-mediated events following an inciting event may take longer to present and be diagnosed. Of note, a reported event of scleroderma in the subject with pre-existing mixed connective tissue disease is not considered new-onset as scleroderma is a characteristic of mixed connective tissue disease.*

In addition to the AESIs described above, the 22 February 2013 CR letter item 2 requested additional information regarding the below subjects enrolled in DV2-HBV-16 with events that may be considered AESIs. The Applicant's responses, submitted in STN 125428/0.34 and 0.35 regarding subjects with AESIs are reviewed here.

Briefly, subject 32-018 (study DV2-HBV-16) was a 43-year-old female with a medical history of depression, bipolar disorder, neck and bilateral arm pain, prior addiction to pain medication, fatigue, and insomnia. Concomitant medications at study entry included an amphetamine (Adderall) for fatigue, temazepam for insomnia, trazodone and venlafaxine for depression, aripiprazole for bipolar disorder, and oxycodone for pain. She was diagnosed with narcolepsy 13 days following her second study injection. She was treated with armodafinil and sodium oxybate. The adverse event was graded as mild in intensity and was deemed unrelated to study vaccine by the investigator. No action was taken regarding further study treatments. Additional information submitted in 125428/0.34 included the source document in which the narcolepsy was first submitted to the site and a note dated three years later (2013) stating that the subject declines to

allow the site to contact her previous PCP for more information, that the subject began having symptoms when she was 13 years of age, but wasn't diagnosed until she was on-study, and that despite discontinuing her treatment due to insurance reasons, she is not currently experiencing symptoms. The Applicant also provided protocol-specified autoimmune laboratory assessments. Anti-dsDNA titers were negative at baseline and end of study. At baseline, the ANA titer was <1:40, and 1:40 with a speckled pattern at Week 52 (study end).

Reviewer comment: *Narcolepsy was not included in the list of AESIs for study DV2-HBV-16, but has since been added to CBER's list due to an evolution in understanding of the disease. However, it appears this subject was experiencing symptoms prior to study enrollment and the diagnosis of narcolepsy is in question given the subject's baseline medications with the potential to disturb sleep and the resolution of her symptoms in the absence of treatment.*

Briefly, subject 21-640 (study DV2-HBV-16) was a 68-year-old female Heplisav-B recipient with a past medical history that included cervical stenosis, laminoplasty and hypertension who developed moderate left hand swelling and aching three days following her first and only study injection. Over the next two months, she also reported general body aches, left foot swelling and bruising, mild pain in her right upper shin. Other symptoms were treated and/or resolved, but her left hand swelling and left hand aching were ongoing at the end of the study. The hand aching, swelling and general aches were assessed by the investigator as possibly related to the study treatment; injections were discontinued due to these events. Additional information submitted in 125428/0.34 and 0.35 included the rheumatologist's note, in which he assessed the subject as having a severe degenerative osteoarthritis of her left thumb with acute symptoms brought about by minor trauma, based upon radiographs and physical exam. ESR and "RA quant" were within normal limits and ANA was negative at the time the subject was evaluated by the rheumatologist. The Applicant reports the study evaluations of autoimmunity as follows: negative anti-ds DNA titers at baseline and end of study, and ANA titer of 1:40 with a speckled pattern at baseline, and 1:80 with a speckled pattern at Week 52 (study end). The site reported contacting the subject two years after the end of the study, at which time she reported being asymptomatic.

Reviewer comment: *The specialist's assessment that this is not an autoimmune event appears reasonable.*

Bell's palsy was the most commonly reported new-onset AESI. Bell's palsy was reported in four Heplisav-B recipients and two Engerix-B recipients in the six-month PSP and mTSP, and in six Heplisav-B recipients and two Engerix-B recipients in the one-year PSP. An additional Heplisav-B recipient reported Bell's palsy in study DV2-HBV-004, a study using the prior formulation not included in the integrated safety populations.

In contrast to many other potentially immune-mediated events, Bell's palsy usually presents acutely and is easily recognized and diagnosed by emergency room and primary care physicians. Therefore, it may be reasonable to consider events reported **both in studies with and without prospective identification of AESIs together. However,** differential times of monitoring adverse events, particularly non-serious AEs means that the further an event occurred from vaccination; the less likely it is to be captured. In the total safety database, including studies that utilized an earlier formulation of Heplisav-B, Bell's palsy was reported in seven Heplisav-B recipients

(0.07%) and two Engerix-B recipients (0.05%). In the Heplisav-B group, subjects reporting Bell's palsy were 31 – 59 years of age; in the Engerix-B group, the two subjects were 29 and 34 years of age. In the Heplisav-B group, subjects reported the onset of Bell's palsy at 9 and 15 days after dose 1, the day of dose 2 (55 days after dose 1), and 169, 171, 255, and 270 days after dose 2; in the Engerix-B group, the two subjects reported Bell's palsy onset at 121 days after dose 2 and 26 days after dose 3. The background incidence of Ball's palsy is estimated to be 13 – 34 per 100,000 per year. In the total submitted safety population, including studies using a prior formulation, the rate of Bell's palsy is slightly higher in the Heplisav-B group compared to the Engerix-B group; the rate of Bell's palsy is higher than the background estimate in both groups.

The etiology of Bell's palsy is not well understood, but proposed pathologic mechanisms include reactivation of a virus, particularly a herpes virus, and reactivation of a virus which in turn may provoke an autoimmune reaction against peripheral nerve myelin, similar to Guillain Barré syndrome. Diabetes may also play a role.[54] An inactivated intranasal influenza vaccine was strongly associated with Bell's palsy and a 30 – 60 day range was identified as the risk window for Bell's palsy following that vaccination.[55] One subject in the Heplisav-B group reported Bell's palsy within this window (55 days after dose 1 and on the day of dose 2).

Reviewer comment: *Bell's palsy is considered an AESI given the possible immune-mediated mechanism. Studies of Heplisav-B other than DV2-HBV-23, did not show an imbalance in events of Bell's palsy between treatment groups. It is possible, that this numerical imbalance in DV2-HBV-23 occurred by chance. It is also possible that Heplisav-B is associated with a small but increased risk of Bell's palsy over an extended period of time (at least one year). Study DV2-HBV-23 was the only study that monitored for non-serious adverse events for one year, perhaps explaining why an imbalance was not observed in previous studies. Of note, Bell's palsy is listed in the Engerix-B package insert as occurring following vaccination in post-marketing safety reports. With the available data, it is not clear whether there may be an association between Bell's palsy and Heplisav-B.*

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events
Please see the review, dated 26 February 2013, of the initial BLA submission.

8.5.2 Time Dependency for Adverse Events
Please see discussions of individual events, in particular, the discussion of the timing of major adverse cardiovascular events (MACEs), including myocardial infarction, with respect to vaccination in 6.3. 12.4.

Reviewer comment: *Although, the 1018 adjuvant may be cleared from the body within days to weeks, the peak SPR of Heplisav-B was observed to be Week 24. Because downstream effects of 1018 adjuvant result in priming of T and B cells against hepatitis B surface antigen, pharmacokinetic measurements do not necessarily reflect the pharmacodynamic activity of this adjuvant. Therefore, there is potential for a prolonged, or later, effect on the immune system beyond the time it is cleared from the body.*

8.5.3 Product-Demographic Interactions

In 125428/0.74, in response to 10 November 2016 CR item 43, the Applicant provided an integrated analysis of safety based upon the CBER-requested safety populations by demographics. Please see Section 8.2.2 for a description of the integrated safety populations by demographic subgroups. As the integrated safety analysis focused on SAEs, SAEs and deaths within demographic subgroups are presented below. Immune-mediated events are not presented here by demographic subgroups as there were few events.

Randomization was stratified by age 18 – 39 and 40 – 70 years. In subjects 18 – 39 years of age SAEs were reported more frequently in the Engerix-B group (2.7% Heplisav-B, 3.6% Engerix-B) and in subjects 40 – 70 years of age, SAEs were reported slightly more frequently in the Heplisav-B group (6.1% Heplisav-B, 5.6% Engerix-B) in the one-year PSP. SAEs in the six-month safety populations were similar between treatment groups. Deaths were more frequently in the Heplisav-B group in subjects 40 – 70 years of age in all integrated safety populations (0.39% Heplisav-B, 0.26% Engerix-B in the one-year PSP). CBER asked the Applicant to present safety by age 18 to 65 years of age and 65 and older. In subjects 18 to 65 years of age, SAEs were reported with similar frequency between treatment groups and deaths were slightly more frequent in the Heplisav-B group in the one-year PSP (0.33% Heplisav-B, 0.21% Engerix-B). Please see the discussion in Section 9.1.5 regarding imbalances in the age subgroup 65 years of age and older. Adjudicated MIs were generally reported more frequently in the Heplisav-B group in all age subgroups evaluated. There was one subject under age 40 who reported an adjudicated MI in the Heplisav-B group.

Reviewer comment: *There are no clear patterns of product-demographic interactions based upon age in the subgroups presented above. In the reviewer's judgement, if Heplisav-B does contribute to MI, there is no safe age at which to administer vaccine, as individuals may be developing coronary artery disease at a young age. The subject younger than 40 years of age who reported an MI provides supportive evidence of this assessment.*

The rates of SAEs were similar between treatment groups when evaluated by sex. Deaths were similar between treatment groups in men, but were more frequent in the Heplisav-B group in women [0.24% (9 subjects) Heplisav-B, 0.06% (1 subject) Engerix-B] in the one-year PSP. When deaths due to trauma or illicit drug overdose are excluded, six Heplisav-B subjects (0.16%) and no Engerix-B subjects died due to causes other than trauma or overdose. All of the deaths in women occurred in study DV2-HBV-23. As reported by investigators, three women died of cardiovascular causes, two women died of unknown causes and one died of small cell lung cancer. As determined by the Applicant's post-hoc blinded adjudicators, two women died of cardiovascular causes
and three died of unknown causes. As a majority of the study populations were white and non-Hispanic, SAEs and deaths in those subgroups reflected the findings in the overall integrated safety populations in that SAEs were similar between treatment groups and deaths occurred more frequently in the Heplisav-B group. In Blacks or African Americans, deaths were reported more frequently in the Engerix-B group [0.22% (4 subjects) Heplisav-B, 0.51% (4 subjects) Engerix-B in the six-month safety populations; 0.4% (7 subjects) Heplisav-B, 0.65% Engerix-B (5 subjects) in the one-year PSP], although there were only a small number of deaths in this subgroup (12 deaths).

SAEs were reported more frequently in the Heplisav-B group in Hispanic subjects in the one-year PSP [6.7% (43 subjects) Heplisav-B, 4.0% (11 subjects) Engerix-B].

Reviewer comment: *It is difficult to draw conclusions for these post-hoc analyses by demographic subgroups, particularly for small subgroups and for low numbers of events (for example, deaths).*

8.5.4 Product-Disease Interactions
The population enrolled in study DV2-HBV-23 was different from the populations enrolled in previous studies, particularly in cardiac disease risk factors. Study DV2-HBV-23 was the only study in which an imbalance in cardiac events, in particular acute myocardial infarction, was observed.

Reviewer comment: *The proposed indication for Heplisav-B in this CR is immunization against all known subtypes of hepatitis B virus in adults 18 years of age and older. An adjuvanted vaccine might be targeted to populations that tend to demonstrate higher rates of non-response to approved hepatitis B vaccines (for example, older individuals, obese individuals, smokers) or to subjects on dialysis who require a higher dose of approved vaccines and yearly confirmation of anti-HBsAg levels. A true safety signal in cardiac events in populations with cardiac risk factors would be concerning, as it is anticipated that those populations would be targeted for vaccination with Heplisav-B.*

8.5.5 Product-Product Interactions
Not applicable.

8.5.6 Human Carcinogenicity
Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Not applicable.

8.5.8 Immunogenicity (Safety)
Please see safety conclusions (Section 8.6).

8.5.9 Person-to-Person Transmission, Shedding
Not applicable.

8.6 Safety Conclusions
The integrated safety analysis conducted by CBER focused on SAEs and AESIs, as these safety outcomes were collected in DV2-HBV-23, the trial submitted in response to the complete response, and overlapped with previous trials. The integrated safety analysis was based on the following three populations: 1) a six-month primary safety population (PSP), including all three pivotal studies; 2) a one-year PSP, including the two pivotal trials that monitored SAEs and AESIs for one year; and 3) a modified total safety population (mTSP), including the five studies that used the proposed formulation of Heplisav-B, that evaluated safety outcomes for six months. The subject population in the mTSP was a similar age and gender composition as the largest pivotal study, DV2-HBV-23. The mTSP had a lower proportion of Black/African American subjects than DV2-HBV-23 and subjects had fewer cardiac risk factors than those enrolled in DV2-HBV-23.

Deaths were balanced between treatment groups in the six-month safety populations (six-month PSP and mTSP), but a numerical imbalance was observed in the one-year PSP, driven by the deaths reported in study DV2-HBV-23. Excluding deaths due to overdose and injury, there were 17 deaths in the subjects who received at least one dose of Heplisav-B (0.23%) and five deaths in subjects who received at least one dose of Engerix-B (0.15%) in the mTSP. SAEs and non-fatal SAEs occurred at similar rates in the Heplisav-B and Engerix-B treatment groups in the integrated safety populations. SAEs in the cardiac system organ class were slightly more frequent in subjects who received Engerix-B in the six-month integrated safety populations, but more frequent in subjects receiving Heplisav-B in the one-year PSP. The imbalance in myocardial infarctions (by SMQ narrow and by Applicant adjudication) that was observed in DV2-HBV-23, was not observed in other studies of Heplisav-B. Given the seriousness of the events of AMI and the magnitude of the imbalance observed in one of the pivotal trials, further evaluation of all cardiac SAEs is required in order to assess the risk benefit profile of the Heplisav-B.

In the two pivotal studies that utilized review of potential AESIs by an expert panel, both demonstrated new-onset diagnoses of immune-mediated adverse events of special interest, including autoimmune events were reported more frequently in the Heplisav-B groups. In DV2-HBV-16 and -23, 15 subjects who received Heplisav-B (0.20%) and one subject who received Engerix-B (0.03%) reported new-onset AESIs (immune-mediated events). One of these subjects in the Heplisav-B group reported an event with an alternative plausible cause. An additional subject in the Heplisav-B group reported a granulomatous dermatitis in DV2-HBV-23, for which systemic disease was not ruled out.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No trials were conducted specifically to assess the safety of Heplisav-B in pregnancy and pregnancy was an exclusion criterion for all clinical trials of Heplisav-B. Limited data are available from subjects who became pregnant after receiving Heplisav-B.

The clinical review of the initial BLA submission contains a discussion of pregnancies reported in the clinical trials conducted prior to the March 2016 resubmission of the BLA.

Information on pregnancies in study DV2-HBV-23 was submitted in 125428/0.42 in the CSR and in 125428/0.67 addressing item 39 of the 10 November 2016 CR. Forty-one pregnancies were reported in 40 subjects (26 pregnancies in 26 subjects in Heplisav-B, 15 pregnancies in 14 subjects in Engerix-B). The pregnancy outcomes in the Heplisav-B group were as follows: healthy term delivery (n = 15), spontaneous abortion (n = 3), induced abortion (n = 2), premature delivery (n = 1), congenital Ebstein's anomaly (n = 1), and unknown (n = 4). One subject reported maternal gestational diabetes and a healthy term delivery. The pregnancy outcomes in the Engerix-B group were as follows: healthy term delivery (n = 8), spontaneous abortion (n = 2), induced abortion (n = 2), fetal complication (n = 1), congenital Ebstein's anomaly (n = 1), and unknown (n = 1). There were no pregnancies reported in study DV2-HBV-22. Narratives for the cases of spontaneous abortion, premature delivery, and Ebstein's anomaly follow.

Subject 106-213 was a 35-year-old woman with medical history of diabetes type 2, morbid obesity, post-traumatic stress disorder, anxiety, depression, irritable bowel syndrome, and one prior spontaneous abortion. She reported concomitant medication of metformin, Levemir (insulin detemir), Bydureon (exenatide), Zoloft (sertraline hydrochloride), Lamictal (lamotrigine), Abilify (aripiprazole), prazosin, and amitriptyline. She had a positive urine pregnancy test 21 days following her second dose of Heplisav-B, 26 days after her last menstrual period (LMP). She reportedly discontinued all medications at this time. Sixteen days later, 42 days after her LMP, she had a spontaneous abortion.

Subject 129-154 was a 30-year-old woman with "three prior pregnancies and one induced abortion." At the Week 24 study visit, a urine pregnancy test was positive. The subject reported bleeding had started the previous day, assumed to be her LMP. Ultrasound demonstrated an empty uterus. No treatment for the spontaneous abortion was given.

Subject 134-047 was a 41-year-old woman with a medical history of headaches, migraines, hypertension, hyperlipidemia, asthma, and uterine fibroids with two prior pregnancies. She had a positive serum pregnancy test approximately nine months after the second dose of Heplisav-B. Approximately one month later no fetal pole was seen on ultrasound and three weeks after that a spontaneous abortion was reported.

Subject 139-119 was a 31-year-old woman taking Effexor (venlafaxine hydrochloride) for depression with two prior pregnancies and one spontaneous abortion. She reported a pregnancy while on study, with an estimated date of conception 45 days after the second dose of Heplisav-B. Placenta previa was diagnosed and she delivered a female infant via C-section at 31 weeks' gestation. At study conclusion, the subject and her infant were reported to be doing well.

Subject 120-019 was a 25-year-old African-American woman with a past medical history of two prior pregnancies (one spontaneous abortion and one prior C-section), urinary tract infection, and morbid obesity. Approximately six months after the second dose of Heplisav-B, the subject had a positive urine pregnancy test. LMP was estimated approximately 4.5 months following dose 2. A first trimester ultrasound revealed a dichorionic/diamniotic pregnancy with intrauterine growth restriction (IUGR) for each fetus and a congenital cardiac anomaly in one fetus. At approximately 36 weeks of gestation, she was admitted to the hospital. An ultrasound at that time revealed both babies with less than the 5th growth percentile and one baby with Ebstein's anomaly. The subject underwent a C-section and delivered a viable male and female infant. No birthweights are reported, but the female infant was noted to be small for gestational age and with a systolic murmur.

In the total safety database of all Heplisav-B studies submitted, the Applicant reports that there were 40 pregnancies reported in Heplisav-B recipients with the following outcomes: healthy term delivery (n = 24), spontaneous abortion (n = 3), induced abortion (n = 4), healthy premature delivery (n = 2), stillbirth (n = 1), congenital Ebstein's anomaly (n = 1), and unknown (n = 5).

Reviewer comment: *Data are insufficient to assess Heplisav-B in pregnancy. There is no evidence that Heplisav-B contributed to the adverse outcome of any pregnancy listed above.*

9.1.2 Use During Lactation
No clinical data are available to address the use of Heplisav-B during lactation.

9.1.3 Pediatric Use and PREA Considerations
Not applicable. Please see the clinical review of the initial BLA submission for a discussion of the Pediatric Research Committee meeting regarding this product.

9.1.4 Immunocompromised Patients
No data have been submitted regarding the safety and immunogenicity of this product in immunocompromised subjects.

9.1.5 Geriatric Use
In the mTSP, the studies which utilized the current formulation of Heplisav-B, 910 subjects 65 – 70 years of age were enrolled and vaccinated with Heplisav-B and 372 were vaccinated with Engerix-B. One subject older than 70 years of age (age 71) was enrolled and vaccinated in study DV2-HBV-23. Immunogenicity data were not analyzed for subjects 65 years of age and older in studies DV2-HBV-10, -16, or -23.

In 125428/0.74, the Applicant submitted an analysis of safety in subjects 65 – 70 years of age. Subjects in this age group in the integrated safety populations were predominantly male (53%), white (91% Heplisav-B, 88% Engerix-B, and not Hispanic (95% Heplisav-B, 94% Engerix-B). Of the risk factors for cardiovascular disease evaluated, the greatest differences between treatment groups were in obesity (47% Heplisav-B, 44% Engerix-B) and type 2 diabetes (24% Heplisav-B, 22% Engerix-B).

In this age group, any SAE was reported in 5.6% of the Heplisav-B recipients and 3.5% of the Engerix-B recipients in the six-month integrated safety populations (six-month PSP and mTSP) and in 10.1% of the Heplisav-B recipients and 7.8% of the Engerix-B recipients in the one-year PSP. A fatal SAE was reported in 0.33% of the Heplisav-B recipients (three subjects) and none of the Engerix-B recipients in the six-month integrated safety populations and in 0.44% of the Heplisav-B recipients (four subjects) and 0.54% of the Engerix-B recipients (2 subjects) in the one-year PSP. Myocardial infarction (by SMQ narrow) was reported by 0.44% (n = 4) of Heplisav-B recipients and no Engerix-B recipients in the six-month PSP and by 0.66% (n = 6) of Heplisav-B recipients and 0.27% (n = 1) of Engerix-B recipients in the one-year PSP. Osteoarthritis SAEs were reported by 0.66% (n = 6) of Heplisav-B recipients (five with a past medical history of osteoarthritis) and 0.27% (n = 1) of Engerix-B recipients (with a past medical history), but non-serious events of osteoarthritis were balanced. The following AESIs were reported by Heplisav-B recipients 65 – 70 years of age: Tolosa-Hunt syndrome, vitiligo, and polymyalgia rheumatica.

Reviewer comment: *A higher frequency of SAEs was reported in Heplisav-B recipients 65 – 70 years of age compared to Engerix-B recipients. As was observed in study DV2-HBV-23, SAEs of MI were reported more frequently in Heplisav-B recipients in the integrated safety population in subjects in this age group. It is possible that other factors contributed to this difference. For example, SAEs were reported more frequently in DV2-HBV-23 in diabetics, which is more prevalent in older individuals.*

9.1.6 Individuals with Chronic Kidney Disease or on Hemodialysis:
Insufficient information regarding the safety and immunogenicity of Heplisav-B are available in individuals with chronic kidney disease or on hemodialysis. See Section 2.4.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered
Not applicable.

10. CONCLUSIONS

The complete response letter issued in February 2013, noted concerns with the size of the safety database for Heplisav-B and the occurrence of two potential serious immune-mediated events in Heplisav-B recipients. In response, the Applicant has submitted study DV2-HBV-23, a large safety study in which 5587 subjects received Heplisav-B and 2781 subjects received Engerix-B and were monitored for one year following second vaccination.

Immunogenicity was comparable to previous studies, although immunogenicity results from those studies were revised by the Applicant in their complete response dated 16 March 2016 based on revised per protocol populations. These results were verified using data submitted by the Applicant in this CR. StudyDV2-HBV-23 confirmed the immunogenicity findings of studies DV2-HBV-10 and -16, and demonstrated that Heplisav-B was immunogenic in all subgroups evaluated, including older individuals, type 2 diabetics and obese subjects. The definition of smoking status precluded clinically meaningful interpretation.

Safety review of study DV2-HBV-23 identified notable imbalances that were not observed in previous studies that enrolled study populations with a lower prevalence of risk factors for cardiovascular disease. In this study, there was an imbalance in cardiac SAEs, in particular in events of myocardial infarction. Serious adverse events with preferred terms in the standardized MedDRA query narrow for myocardial infarction were reported in the Heplisav-B group at approximately three times the rate reported in the Engerix-B group. A numerical imbalance in deaths trending in the same direction was also observed. The study was randomized and as expected, prevalences of cardiovascular risk factors and history of ischemic cardiac disease were balanced between treatment groups at baseline. Imbalances were also noted in medically attended events of herpes zoster in study DV2-HBV-23. To further evaluate the cardiac imbalances, the Applicant submitted a post-hoc major adverse cardiovascular events (MACE) analysis that included blinded adjudication of events of cardiovascular death, myocardial infarction, and stroke. Based upon these adjudications, in study DV2-HBV-23, myocardial infarction was reported in the Heplisav-B group at almost seven times the rate reported in the Engerix-B group. A small imbalance in adjudicated stroke trended unfavorable to Heplisav-B. There were few events in both groups adjudicated as cardiovascular death, but seven events in the Heplisav-B group were adjudicated as not enough information to determine the cause of death. The imbalance in MI in the Heplisav-B group is observed at approximately two months after the second vaccination and persists through the remainder of the study. While it is possible that these differences may have occurred by chance, it is the assessment of the clinical reviewer that, due to the magnitude of the imbalance and the similar trend of other cardiovascular events (death and stroke), the possibility that this difference did not occur by chance has not been adequately ruled out.

In two of the pivotal studies and one supportive study, adverse events of special interest were prospectively defined by a list of conditions that CBER considers potentially immune-mediated. Events identified as potential AESIs by investigators were referred to a specialist and an adjudication committee in studies DV2-HBV-16, -22, and -23. The SEACs adjudicated eight events as autoimmune AEs, all reported in the Heplisav-B groups. The SEAC assessed none of these events as related to vaccination. Additional events (Bell's palsy and erythema nodosum) were new in onset, not adjudicated by the SEAC as autoimmune events, but are considered AESIs by CBER. One of these events, erythema nodosum, was assessed by the SEAC as related to vaccination. Based on SEAC-confirmed diagnoses, new-onset AESIs without alternative plausible causes as assessed by the reviewer, were identified in 14 subjects in the Heplisav-B group (0.18%) and 1 subject in the Engerix-B group (0.03%). In studies that did not prospectively define and monitor AESIs, retrospective analysis of preferred terms on the AESI list were reported less frequently in the Heplisav-B groups compared to the Engerix-B groups. Two rare serious inflammatory vascular conditions with a granulomatous (granulomatosus with polyangiitis in study DV2-HBV-10, background incidence 1-3 per 100,000) or presumed granulomatous (Tolosa-Hunt syndrome DV2-HBV-16, background incidence 1 per 100,000,000) pathology were identified following Heplisav-B vaccination. An additional event of granulomatous dermatitis, a rare autoimmune skin condition often concurrent with systemic immune-mediated disease, was also reported in study DV2-HBV-23. The SEAC did not agree with the diagnosis, and thus this event is not reflected in the numbers above. However, the reviewer assesses this a new-onset autoimmune disease with potential connections to the other granulomatous or presumed granulomatous conditions identified in the safety database. The number of potentially immune mediated events was small. With the exception of the granulomatous diseases and several events of Bell's palsy, events were from different organ systems and generally represented different pathophysiologies. However, as the imbalance is noted across two studies and given the very low likelihood of more than one rare condition being diagnosed within the pre-licensure safety database, risk of autoimmune disease associated with Heplisav-B remains a potential risk.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 49. Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute HBV infection may cause subclinical hepatitis, icteric hepatitis, or fulminant hepatic failure. • Chronic hepatitis B infection can cause a chronic carrier state or progress to hepatic cirrhosis, liver failure, and death. • Globally, there are more than 250 million HBV carriers.[3] • In the U.S., hepatitis B vaccination was incorporated into the routine childhood immunization schedule in 1992, which has resulted in a significant decline in the rate of acute HBV infection. The incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.1 per 100,000 (2015). The greatest decrease (96%) has been reported among infants and adolescents. The age group with the highest incidence of acute hepatitis B in the U.S. is 30-39 years.[4] • Chronic hepatitis B has been reported at an incidence of 7.6 cases per 100,000 in 2015. In cases for which place of birth was known, the majority of individuals were born outside of the U.S. (74.6%). Approximately one third of new cases occurred in adults 25-39, one third in adults 40 – 54, and one quarter in adults 55 years and older.[4] The risk for chronic HBV infection decreases the older individuals are at time of infection. Approximately 5% of acute hepatitis B infections progress to chronic infection in adults.[3] • Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S., when known, transmission is primarily sexual or by injection drug use.[4] • Nosocomial transmission between patients and from patients to health care workers, including in the setting of hemodialysis (HD) and oncology units, have declined since implementation of routine vaccination and standard precautions for blood-borne pathogens. The seroprevalence of HBs antigen among hemodialysis patients was 1.0% and the incidence of HBV infection among these patients was 0.12% in 2002.[5] In 2015, of the case reports that included information about receipt of dialysis or kidney transplant, 0.2% of persons with acute hepatitis B infection reported receipt of dialysis or kidney transplant.[4] • In 2015, the CDC reported 1,715 deaths in the U.S. noting hepatitis B as an underlying cause.[4]	• Chronic hepatitis B remains a major worldwide public health challenge, with the majority of individuals affected, of Pacific Islander/Asian ethnicity. • Acute hepatitis B infection is declining in the U.S. in association with universal childhood vaccination. • The majority of acute hepatitis B cases in the U.S. do not progress to chronic hepatitis B. • Chronic hepatitis B incidence decreases as the age at which a person is infected increases, and is relatively rare in adults born in the U.S. Based on the available data, most cases of chronic hepatitis B reported in the U.S. occur in individuals born outside of the U.S. • Hepatitis B incidence in at-risk individuals such as hemodialysis patients, immunosuppressed patients (oncology units), and healthcare workers has been steadily decreasing, due to implementation of routine vaccination and standard precautions. Injection drug use (IDU) remains an important risk factor for transmission of hepatitis B infection.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	• Two licensed vaccines are currently available for the prevention of HBV in adults and adolescents in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). • There is one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. • Engerix-B, Recombivax HB, and Twinrix are each administered as a three-dose series, at months 0, 1, and 6. • A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. • An accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12. • These vaccines have been shown to be highly effective in controlled clinical trials evaluating the antibody response against hepatitis B surface antigen. • Special populations that have been historically categorized as hyporesponders include the following groups: non-responders to hepatitis B vaccine, and immunosuppressed individuals (such as those with poorly-controlled diabetes, chronic kidney disease and on hemodialysis). • Chronic HBV infection in immunized people has been documented in dialysis patients whose anti-HBsAg antibody concentrations fell below 10 mIU/mL. For adults on dialysis, formulations of Recombivax HB and Engerix-B containing 40 mcg HBsAg per dose (standard adult dose is 10 or 20 mcg of HBsAg, respectively) administered in a 3 or 4 dose series, respectively, are approved. • The higher antigen dose regimen of hepatitis B vaccine (dialysis regimen) may also be considered for those individuals with immunosuppression due to other causes and those deemed hypo-responsive to standard hepatitis B vaccine regimens. Booster vaccination may be administered, if indicated, and is generally associated with significant levels of seroconversion in hyporesponsive individuals.[56] • Long-term studies indicate that immune memory to hepatitis B post-vaccination remains intact for up to two decades post-immunization, even though anti-HBs antibody concentrations may become low or undetectable over time.[57] • Compliance with vaccination is determined by multiple factors and appears to be a greater problem in the adolescent population than in adults ≥ 30 years of age, as based, on a large, multisite, retrospective cohort study of older children, adolescents, and adults in the Vaccine Safety Datalink population from 1996 through 2004.[58]	• Several effective hepatitis B vaccines are currently licensed in the U.S. that offer long-term protection against hepatitis B in immunocompetent adults. • Engerix-B and Recombivax HB also have immunization schedules for renal dialysis patients. • In adults, currently approved vaccines require at least three doses. • A vaccine against hepatitis B that improves immunogenicity in certain populations (for example, those reported to be hypo-responsive to currently available vaccines) or that utilizes a shorter immunization schedule (for example: for naïve individuals who require rapid induction of anti-hepatitis B antibodies due to travel to areas endemic for hepatitis B), may represent an unmet medical need. • The Applicant did not submit to the BLA data to support use of Heplisav-B in the CKD and hemodialysis population. • Although breakthrough infections (detected by presence of anti-HBc antibodies or HBV DNA) have occurred in immunized individuals, in immunocompetent persons these infections are transient and asymptomatic.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Heplisav-B vaccine, given as an intramuscular (IM) injection at Week 0 and 4 resulted in greater than 85% of healthy adult study subjects being seroprotected (as defined by an anti-hepatitis B antibody level ≥ 10 mIU/mL) at one month after the second dose of Heplisav-B and anti-hepatitis B antibody levels remained at or above seroprotective levels for a 28-week period post-vaccination (study DV2-HBV-10). • Geometric mean antibody concentrations measured against hepatitis B surface antigen in Heplisav-B vaccinated adult subjects showed a mean increase to 41.5 mIU/mL, approximately one month after completion of the vaccination series (at Week 8). GMCs peaked at a mean GMC of 232.7 mIU/mL at approximately Week 24 (20 weeks after completion of the vaccination series), and remained above 10 mIU/mL (the seroprotective level) at a mean GMC of 150.7 mIU/mL at Week 52 (48 weeks after completion of the vaccination series) (study DV2-HBV-16). • The seroprotection rate (SPR) following two doses of Heplisav-B was non-inferior to the SPR rate induced by three doses of an active comparator, Engerix-B (studies DV2-HBV-10 and -16). • Evaluation of the SPR at Week 28 after vaccination with the two-dose series of Heplisav-B demonstrated a robust immune response in type 2 diabetics taking an oral or non-injectable hypoglycemic agents and/or insulin — a population identified by the Applicant as hyporesponsive to available vaccines (study DV2-HBV-23). • In vaccine efficacy studies, immunocompetent individuals who developed anti-HBs antibody concentrations ≥ 10 mIU/mL after vaccination had virtually complete protection against both acute and chronic hepatitis infection, even if anti-HBs concentrations subsequently declined to < 10 mIU/mL.[57] • Protection to hepatitis B infection despite a decline in anti-HBs to < 10 mIU/mL is thought to be due to preservation of immune memory through selective expansion and differentiation of clones of antigen-specific B and T lymphocytes.[57]	• Heplisav-B demonstrated a rapid and robust immune response against hepatitis B surface antigen, as shown by anti-hepatitis B geometric mean antibody concentrations and SPR. • The GMCs and SPR of Heplisav-B were shown in clinical trials to be noninferior to an active comparator, Engerix-B, when compared at week 32 after initiation of the immunization series. • Anti-HBs antibody levels (GMCs) remain at protective levels for at least 48 weeks after completion of the Heplisav-B vaccination series (≥ 10 mIU/mL). • Even with anti-HBs levels < 10 mIU/mL, vaccine efficacy studies in immunocompetent adults indicate protection against both acute and chronic hepatitis B infection, most likely due to the anamnestic immune response and preservation of immune memory. Therefore, elevated GMCs against HBsAg beyond the seroprotective cutoff are not indicative of greater effectiveness or protection against hepatitis B infection.[57] • Higher GMCs might afford a longer duration of protection against hepatitis B, when taking into account the effect of antibody decay pharmacokinetics in plasma (i.e. starting at a higher initial anti-HBs antibody level).

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• Heplisav-B contains a novel cytosine phosphoguanine adjuvant, 1018, which is a toll-like receptor 9 (TLR9) agonist. TLR agonists activate the innate immune system, specifically those pathways with Th1 pro-inflammatory effects. • In a large, randomized, controlled, pivotal, safety trial with a population that was at greater risk of cardiovascular disease than previous studies, acute myocardial infarction (MI) was more frequent in the Heplisav-B group compared to the Engerix-B group. Serious adverse events identified by the standardized MedDRA query narrow for MI were reported in 19 Heplisav-B subjects (0.3%) and 3 Engerix-B subjects (0.1%) (RR = 3.152, 95% Koopman score CI 1.00, 9.98). MIs identified by the Applicant's blinded, post-hoc adjudication were reported in 14 Heplisav-B subjects (0.3%) and one Engerix-B subject (0.04%) (RR = 6.97, 95% Koopman score CI 1.17, 41.44). Adjudicated stroke trended in the same direction. There were few adjudicated cardiovascular deaths. The difference between groups in MACE events was observed at 2 months following the second vaccination and persisted for the duration of the one-year study follow-up (study DV2-HBV-23). Prior studies did not show a similar imbalance in MI. • The subpopulations for which Heplisav-B might afford benefit in terms of inducing a vigorous immune response (i.e. older adults, the obese, diabetics, smokers, patients with chronic kidney disease) are the same subpopulations with increased cardiovascular risk factors; which may increase the risk of an adverse cardiac outcome after vaccination with Heplisav-B. • As the full mechanism of action of the 1018 adjuvant is unknown, there are theoretical concerns it could contribute to certain disease processes, such as autoimmunity. • In the two pivotal and one supportive trials (DV2-HBV-16, -22, -23) that utilized expert adjudication of adverse events of special interest (AESIs), new-onset adjudicated immune-mediated events without alternative plausible causes were more frequent in the Heplisav-B group (14 subjects, 0.18%: Bell's palsy in 6 subjects, hypothyroidism in 2 subjects, and 1 subject each with alopecia areata, erythema nodosum, polymyalgia rheumatica, Tolosa-Hunt syndrome, ulcerative colitis, vitiligo) compared to the Engerix-B group (1 subject, 0.03%: Bell's palsy). An additional subject reported granulomatous dermatitis, for which an evaluation for sarcoidosis, a systemic granulomatous disease, was recommended by the dermatopathologist but not performed. Prior studies that did not utilize an adjudication process did not show an imbalance in AESIs unfavorable to Heplisav-B. Notably, two granulomatous or presumed granulomatous angiopathies, Tolosa-Hunt syndrome (identified in DV2-HBV-16) and granulomatosis with polyangiitis/Wegener's granulomatosis (identified in the pivotal trial without prospective monitoring of AESIs, DV2-HBV-10) were reported in two subjects without prior autoimmune disease after Heplisav-B vaccination. • In study DV2-HBV-23, Herpes zoster was reported in more frequently in subjects who received Heplisav-B (0.68%) compared to subjects who received Engerix-B (0.32%). • Common reactions to Heplisav-B included increased redness and swelling in subjects who received Heplisav-B compared to subjects who received Engerix-B. These injection site reactions were generally mild to moderate.	• An increased frequency of myocardial infarction was observed in one large randomized safety study in a population enriched with cardiovascular risk factors. A related cardiovascular event (stroke) trended in the same direction. While the total number of events was small, the difference between groups was substantial. The possibility that this represents a real increase in risk associated with Heplisav-B was not adequately ruled out. • The occurrence of two rare granulomatous vasculitides following vaccination as well as an increased frequency of adjudicated potentially immune-mediated disorders, may represents a small, but clinically significant risk. • An increased risk of herpes zoster may represent a clinically significant risk and warrants further evaluation. • Solicited adverse reactions did not raise safety concerns.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The Applicant is seeking an indication for use in the general adult population with no upper age restriction. • ACIP recommends that hepatitis B vaccination should be administered to all unvaccinated adults at risk for hepatitis B infection, requesting protection from hepatitis B virus, or with diabetes who are younger than 60 years, and they recommend vaccination may be administered to unvaccinated adults with diabetes who are 60 years of age and older taking into consideration their risk of acquiring HBV, risk of experiencing sequelae of HBV infection, and likelihood of immune response to vaccination. It is reasonable to assume that these populations would be targeted to receive Heplisav-B, if approved. • Many individuals theoretically most likely to benefit from the robust immune response generated by Heplisav-B are likely to also be at increased risk for cardiovascular disease. • Risk of MI increases with age. However, in DV2-HBV-23, two Heplisav-B recipients and no Engerix-B recipients younger than 50 years of age had adjudicated MIs, including one subject younger than 40 years of age. Furthermore, younger subjects are less likely to benefit with Heplisav-B over existing therapies compared to older subjects. • Subjects at risk of immune-mediated diseases are difficult to identify. A study to evaluate an increased risk of very rare diseases would require an extremely large study population and likely take a significant amount of time before results were available. • Factors that may contribute to increased risk, for both cardiovascular disease and autoimmune disease, in any given individual are likely multifactorial, additive, and may include additional risk factors not assessed in the analyses conducted to date with Heplisav-B. Even in seemingly healthy individuals, significant cardiac risk factors or underlying risk for autoimmune disease can be present. • Other risk mitigation strategies that are available, such as increased monitoring of recipients, are not appropriate or feasible in the setting of a vaccine to prevent, not treat, disease. • A post-licensure study of cardiovascular risk is likely to require at least a year for results to be available. Potential restrictions in the vaccine's indication for use, if approved, would affect the ability to draw conclusions from these data. If only individuals at very low risk for cardiovascular events receive the vaccine, a much larger study would be required to adequately evaluate increased risk associated with the vaccine.	• Due to the low total number of events, and potential incomplete ascertainment of both events and risk factors for cardiovascular disease, it is difficult to draw strong conclusions regarding cardiovascular risk in subgroups based on the available data. • Limiting use to a particular subgroup based on age or other risk factors for cardiovascular disease may not adequately reduce the potential risk and may not be feasible in the setting of a preventive vaccine. • There is no mechanism currently available to determine on an individual patient basis, all the underlying risk factors that could or would contribute to an adverse cardiovascular or autoimmune outcome after administration of this vaccine. • Prospective screening of otherwise healthy individuals for cardiovascular risk factors, simply to determine whether they are an appropriate candidate to receive a preventive vaccine for which licensed alternatives exist, may be cumbersome in clinical practice and thus, not be realistic. • It is unlikely that restricting usage to adults who are younger than a specified age will mitigate the potential risk of immune-mediated conditions. • Post-marketing evaluation may be limited in its ability to provide appropriate consent of subjects, to adequately account for differences in treatment groups, and to obtain the necessary follow-up to capture all events of interest. It will also be ongoing while the vaccine is available to the general public.

11.2 Risk-Benefit Summary and Assessment

Heplisav-B has the potential to provide a clinical benefit due to the immunogenic properties of the vaccine. The immunogenicity data submitted to this BLA provide evidence that Heplisav-B demonstrates a rapid, robust, and sustained immune response, based on evalulation of the proportion of subjects with an anti-hepatitis B antibody concentration ≥ 10 mIU/mL, the level recognized as conferring protection against HBV infection. The immune response to Heplisav-B after the second dose was non-inferior to the immune response to Engerix-B after the third dose, in phase 3 studies. A two-dose series that results in a non-inferior immune response represents a clinical benefit. Theoretically, this vaccine has the potential to address what may be considered an unmet medical need in subgroups that have been reported to have a less robust response to currently licensed products, or in those requiring more rapid protection.

Assessment of solicited local and systemic events and unsolicited adverse events was conducted as part of the initial BLA review and did not raise safety concerns based on the available data at that time, as described in detail in the clinical review dated 26 February 2013. More subjects receiving Heplisav-B reported injection site redness and swelling than did subjects receiving Engerix-B. Most redness and swelling was reported as mild or moderate in intensity. The risk of these common reactions was assessed as acceptable.

The initial BLA review did, however, raise concerns over the size of the small safety database for a novel immunostimulatory adjuvant and the occurrence of two inflammatory granulomatous (demonstrated or presumed) vasculitic diseases reported following vaccination with Heplisav-B. These concerns led to an additional safety study, which is the major topic of the current BLA review.

The information included with this BLA resubmission, demonstrates a small but increased risk of adverse events of special interest (AESIs), events that are potentially immune-mediated, following Heplisav-B administration. Retrospective identification of AESIs in studies that did not monitor specifically for these events prospectively did not reveal an imbalance in events unfavorable to Heplisav-B. However, in the studies in which adverse events of special interest (AESIs) were evaluated prospectively and adjudicated by an expert panel, adjudicated new-onset autoimmune events were reported exclusively in the Heplisav-B group. When events with a confirmed (by expert-panel) diagnosis that are considered immune-mediated conditions are included, the proportion of subjects receiving Heplisav-B and reporting such events was approximately six times that of subjects receiving Engerix-B and reporting such events. While the number of events is small, in both pivotal trials with prospective monitoring they occurred more frequently in the Heplisav-B group. One event of erythema nodosum was determined to be related to vaccination by expert adjudication.

The information reviewed with these BLA resubmissions did not alleviate concerns regarding the rare serious immune-mediated events following Heplisav-B administration that were based on adverse events in the Heplisav-B safety database at or before the initial BLA review. One event of granulomatosis with polyangiitis (GPA, formerly, Wegener's granulomatosis) was diagnosed in a subject with laboratory evidence of auto-antibodies (c-ANCA) turning positive and increasing shortly following vaccination. The initial BLA review identified another subject with a possible diagnosis of Tolosa-Hunt syndrome (THS). THS is a painful ophalmoplegia resulting from granulomatous inflammation of the cavernous sinus. Since the initial review, several external CBER consultants confirmed the diagnosis of THS based on the clinical information. One subject in the Engerix-B group reported a p-ANCA positive vasculitis. This subject had a 10-year history of mixed connective tissue disorder and a strongly positive ANA at baseline, indicating that this event may be part of a process that was underway prior to study

enrollment, although the subject's baseline p-ANCA was negative. While there were no clear diagnoses of new-onset systemic granulomatous diseases or vasculitides in the large safety study, one subject reported granulomatous dermatitis for which sarcoidosis was a primary differential diagnosis proposed by treating physicians that was not further evaluated. This event was adjudicated as not autoimmune by the SEAC. However, granulomatous dermatitis may be part of autoimmune-related granulomatous dermatitis that is often concurrent with systemic immune-mediated disease. In the opinion of the clinical reviewer, this may represent a third new-onset systemic granulomatous disorder. The background incidence of GPA and of THS are estimated to be 1:100,000 and 1:1,000,000. Even without considering the case of granulomatous dermatitis, two rare granulomatous angiopathies following vaccination in a safety database of approximately 10,000 is highly unlikely to have occurred by chance and, in the judgement of the clinical reviewer is likely to represent a serious clinically significant risk.

The large safety study identified additional potential risks. An increased frequency of acute myocardial infarction in Heplisav-B recipients compared to Engerix-B recipients was observed in study DV2-HBV-23. The risk of MI persisted in the Applicant's adjudicated analysis of major adverse cardiovascular events and the risk of stroke trended in the same direction. The number of adjudicated cardiac deaths was small. However, including deaths that were adjudicated as insufficient information to determine a cause of death, which are often cardiovascular in nature, results in a greater imbalance unfavorable to Heplisav-B. With the exception of a numerical imbalance in pulmonary embolism noted in the initial integrated safety analysis and not observed in DV2-HBV-23 or the current integrated safety analysis, an increased risk of cardiovascular disease was not observed in prior studies. However, DV2-HBV-23 was a large study with an enriched population with greater proportions of subjects with risk factors for cardiovascular disease compared to other trials of Heplisav-B. It is plausible that a real and clinically significant increased risk might only be observed in a trial such as this. The randomized and controlled study design with balanced cardiovascular risk factors between treatment groups adds to the concern regarding this potential safety signal.

The finding of increased cardiovascular events associated with Heplisav-B was unexpected. If the association is real, the temporal relationship of MACE outcomes and vaccination (divergence in risk between treatment groups is apparent at approximately 70 days post-second vaccination and persisting throughout the study) suggest that Heplisav-B affects a long-term process. Two possible mechanisms suggested by CBER's cardiology consultants include rapidly accelerated atherosclerosis or plaque destabilization/thromboembolism. In the laboratory sub-study of DV2-HBV-23, there was a small but increased rate of subjects with abnormal beta 2 glycoprotein IgM at 4 weeks following dose 2 of Heplisav-B compared to subjects who received Engerix-B. However, the reviewer did not identify any subjects with elevated levels who reported arterial or venous thromboembolic events, and two subjects who reported possible arterial thrombotic events (one with MI and one with MI, left ventricular thrombus, and pulmonary embolism) and participated in the sub-study did not have abnormal levels of anti-beta 2 glycoprotein IgM. While, these findings are difficult to interpret, there was no link identified between antiphospholipid antibody levels in this study and thrombotic events.

There are several limitations of study DV2-HBV-23 with regard to its ability to evaluate the potential cardiovascular signal. Most notably the study did not prospectively evaluate cardiovascular events and thus, it is likely that events were missed. However, given the study was blinded, missed events are likely to have occurred in both treatment groups. The clinical reviewer agrees with other experts (VRBPAC, CBER consultants) who have stated that in order to determine if the imbalance in MI and other cardiovascular events observed in DV2-HBV-23 represents a real increased risk associated with Heplisav-B further study is warranted. The

reviewer thinks that, given the seriousness of the outcomes of interest (myocardial infarction and death), the need to evaluate the risk in a high-risk population and importance of informed consent, and the limitations of observational study designs, the evaluation of cardiovascular risk associated with Heplisav-B should only be considered in a pre-licensure setting with a randomized controlled trial.

In study DV2-HBV-23, a statistically significant increased frequency of non-serious medically-attended herpes zoster was also observed in the Heplisav-B arm. While it is possible that this difference between treatment groups occurred by chance, this imbalance is interesting in the context of other possible risks of the vaccine. Herpes zoster is a possible etiology of Bell's palsy and has been implicated in the occurrence of vasculitides. An increased risk of MI has been observed following herpes zoster;[59] however, in the one subject who reported both events in study DV2-HBV-23, the two events are not closely temporally linked.

In summary, Heplisav-B is a preventive vaccine and, if approved for the proposed indication, may be administered to the general population of adults at risk of hepatitis B infection. There are safe and effective licensed vaccines for the prevention of hepatitis B infection. Benefits that Heplisav-B offers over existing therapy are a two- versus three-dose regimen and the potential for a robust immune response in certain subgroups that have been reported to respond less effectively to approved products. However, the subgroups in which the vaccine has the potential to offer the greatest benefit (for example, older adults, diabetics) are also subgroups at increased risk of cardiovascular disease. Cardiovascular disease, in particular myocardial infarction, was identified as a potential serious risk of Heplisav-B, which the clinical safety reviewer concludes should be further evaluated prior to approval. For other groups in the general adult population, (for example adults younger than 40 years of age), for whom there are effective products for hepatitis B virus prevention, the clinical reviewers do not find that the benefit of a two- versus three-dose series outweighs the potential serious risks identified in clinical trials – immune-mediated diseases, specifically systemic granulomatous diseases, and cardiovascular diseases. The clinical review team could not identify a risk-mitigation strategy that was both feasible and practical to implement to ensure the safe use of this preventive vaccine. In the judgement of the clinical reviewers, the overall risk-benefit of Heplisav-B is not favorable to support licensure for the proposed indication for use in adults 18 years of age and older.

11.3 Discussion of Regulatory Options

Possible regulatory options available to CBER are approval, approval with a post-marketing requirement or commitment, issuance of a complete response, and a recommendation against approval.

As discussed above, given the potential risks of cardiovascular and immune-mediated events and the limited benefit in the context of a preventive vaccine with other available effective products, the reviewer does not consider the risk-benefit profile favorable for approval in the general population.

In theory, CBER might approve the product for a particular subpopulation at low risk for cardiovascular events and to include a description of the observed imbalances in the package insert. Restricting the population of use by age is the most feasible way to accomplish this. Two Heplisav-B recipients and no Engerix-B recipients younger than 50 years of age, one of them younger than 40 years, reported adjudicated MIs. CBER could also consider restricting use by other risk factors for cardiovascular disease (for example, in subjects without diabetes or without hypertension). However, due to the low total number of cardiovascular events, and

potential for incomplete ascertainment of risk factors for cardiovascular disease, it is difficult to draw strong conclusions regarding cardiovascular risk in subgroups with the available data. Furthermore, restrictions for use for a preventive vaccine based on disease may not be feasible in a real-world setting. In the clinical reviewer's opinion, if the cardiovascular signal is real, no restriction of use would sufficiently change the risk-benefit profile to favorable for Heplisav-B.

Two additional options CBER might consider are 1) further evaluation of the potential risks following approval with a post-marketing requirement or commitment or 2) requiring further pre-market evaluation through issuing a complete response. In order to adequately evaluate the potential risk of cardiovascular events following Heplisav-B administration, a pre- or post-marketing trial would require a randomized, blinded, controlled study that prospectively assesses events of interest in appropriately consented subjects. Events of interest may include all three elements of the MACE outcome evaluated post-hoc in DV2-HBV-23, but should definitely include an assessment of MI. In the opinion of the clinical reviewer, evaluation of cardiac ischemic events not meeting the criteria of MI would strengthen the evaluation of this signal (for example, coronary revascularization). Selection bias would be a limitation for an observational post-marketing study given the difference in observed cardiovascular events between treatment groups would be described in the package insert and subjects or providers may self-select treatment group. VRBPAC members stated that any evaluation of the cardiovascular signal should be conducted in a population at-risk for cardiovascular disease. Studies that evaluate cardiovascular risk in a low-risk population are likely to require very large numbers in order to demonstrate a difference in risk or to be potentially falsely reassuring if the study is not appropriately powered. The clinical reviewer also views the informed consent process as very important for any subjects participating in a study to evaluate this safety signal. For these reasons, the reviewer recommends any assessment of cardiovascular risk associated with Heplisav-B be conducted prior to licensure.

21 CFR 601.4(b) outlines the process for denial of licensure, "If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to 12.21(b) of this chapter." The reviewers recommend denial of licensure of Heplisav-B based on an unfavorable risk benefit profile for a preventive vaccine in the proposed population of adults 18 years of age and older.

11.4 Recommendations on Regulatory Actions
The clinical reviewers do not recommend approval of Heplisav-B.

11.5 Labeling Review and Recommendations
As discussed in Section 11.2 – 11.4, the reviewers do not recommend approval of Heplisav-B for the prevention of infection caused by all known subtypes of hepatitis B virus for adults 18 years of age and older. However, at the time of finalizing this review, it appears Heplisav-B will be approved for the indication and population stated. The reviewers participated in labeling discussions and recommended multiple changes, particularly to Section 6, Adverse Reactions, and Section 14, Clinical Studies. Our major recommendations are listed here:

- The reviewers do not agree with the omission of an upper age restriction, as only one subject older than 70 years of age (71 years of age) was vaccinated with Heplisav-B in the safety database submitted to this BLA. One subject is not sufficient to evaluate

safety or immunogenicity in this age group, particularly given the safety signal of myocardial infarction identified in this review.

- The review team did not recommend a statement be included in Section 5, Warnings and Precautions, regarding the safety signal of MI that was observed in DV2-HBV-23. The purpose of this section is to identify subjects that might be at risk of a particular adverse reaction and to offer the provider means of mitigating the risk. The reviewers did not identify an effective and feasible mitigation strategy for MI in the setting of this preventive vaccine. Based on the available data, the reviewers determined there was not a well-defined group for which the vaccine would be safe, and thus, did not identify patient qualities that should contraindicate administration of Heplisav-B with regard to MI. For these reasons, the reviewers could not recommend a specific mitigation strategy to be included in this section.
- The reviewer recommended solicited adverse reactions, unsolicited adverse reactions, serious adverse events, and adverse events of special interest be presented separately for each study because study populations and methods of monitoring and evaluating these events varied significantly between studies.
- The reviewer recommended language regarding immune-mediated adverse events that were identified by the Applicant, based upon SEAC review and the AESI list that was pre-specified in two of the three pivotal trials. The package insert (PI) at the time this review was finalized, describes only events determined to be autoimmune by the SEAC, not all AESIs. Specific language was suggested regarding the case of p-ANCA-positive vasculitis reported in a subject who received Engerix-B in study DV2-HBV-10. While, the reviewer does not disagree with the statement regarding the SEAC's assessment of relationship of autoimmune events in studies DV2-HBV-16 and -23, the following information relevant to the medical provider is missing: 1) one non-autoimmune AESI that the SEAC assessed as possibly related was not included in the PI (erythema nodosum), 2) the reviewer does not agree the Tolosa-Hunt syndrome was not related and the statement that it was not considered related is missing attribution, and 3) no assessment of relationship was presented for the events in DV2-HBV-10, in particular for the event of GPA that the investigator assessed as related.
- The reviewer recommended the following language regarding the safety signal of myocardial infarction, intended to present the number of adjudicated events of MI:

  "Acute myocardial infarction (AMI) occurred in 0.3% (n=14) of HEPLISAV B recipients and < 0.1% (n=1) of Engerix-B recipients (Relative Risk=6.97, 95% Confidence Interval 1.17, 41.44). Among HEPLISAV-B recipients, one event of AMI occurred within 3 days, seven events within 28-180 days, and six events greater than 180 days following any active dose. All events occurred in subjects with one or more baseline risk factors for cardiovascular disease. "

  The reviewer does not agree with the statement in the PI at the time this review was finalized, saying "These and additional analyses did not support a causal relationship between HEPLISAV-B administration and AMI."

- Given that CBER asked the Applicant to include information on immunogenicity in the diabetic subpopulation and by age groups in the package insert (PI) (see below), the reviewer recommended safety information in these subgroups also be presented. Immunogenicity data for geriatric subjects 65-70 years of age (n=910) was summarized in the geriatric section of the package insert but data for individuals 70 years and older was not presented, as the data were insufficient for this age group; only one subject

older than 70 years of age had immunogenicity data collected and evaluated. The reviewers recommended safety data be included for subjects 65 through 70 years of age in section 8.5, Geriatric Use. The reviewer does not agree that safety in subjects older than 70 years can be extrapolated from the available data.

- The reviewer recommended language regarding insufficient evidence to inform vaccine-associated risk in pregnancy, consistent with the Pregnancy and Lactation Labeling Rule.
- The reviewers recommended immunogenicity be presented in text, instead of tabular form. The reviewers additionally recommended that discussion of SPR data by study visit not be included, and that no reference to superiority testing or superiority claims be included in the PI, including statistical criteria for superiority, or discussion of statistically significantly higher SPRs, since there was no evidence in either treatment group of breakthrough infection or disease and thus no evidence of clinically relevant superiority.
- As diabetics were a pre-specified subpopulation for study DV2-HBV-23, the reviewer concluded that inclusion in the PI of the immunogenicity data for this subgroup would be informative to prescribers.
- Presentation of subpopulation data for immunogenicity by age stratification was deemed reasonable by the reviewer, as SPR data varied by age group and was generally lower in older individuals. Stratification by age was deemed clinically relevant and beneficial in informing the degree of protection afforded by Heplisav-B in older individuals. Conversely, presentation of immunogenicity data by sex, race, BMI index (obesity vs. non-obese) and smoking status was not recommended, as these data did not differ significantly across these groups. In the specific case of smokers, this subgroup was not adequately defined to make meaningful inference based on the SPR data provided.
- In currently licensed products, immunogenicity in the population of subjects on hemodialysis is described and this population is a group that receives frequent booster vaccinations for prevention of hepatitis B virus infection. In the initial BLA submission in April 2012, the Applicant submitted study synopses of studies conducted in subjects on hemodialysis and/or with chronic kidney disease (CKD). However, datasets were not submitted in this BLA and CBER is unable to confirm these results or to fully assess safety in these populations. The reviewer recommended that language be included in the PI in Section 8 (Special Populations) to state that data are insufficient in the subpopulation of CKD and hemodialysis subjects.

11.6 Recommendations on Postmarketing Actions

In the judgement of the clinical reviewer, a post-marketing study is unlikely to adequately address the question of whether the increased rate of myocardial infarction observed in study DV2-HBV-23 is real for the reasons described in Section 11.2. Specifically, a study conducted in the post-marketing setting will not be able to adequately consent subjects and to sufficiently control for potential differences in study populations. It is the opinion of the clinical reviewer that any study to attempt to address this safety signal should be randomized and powered to rule out an elevated relative risk (relative risk greater than 1) of myocardial infarction with a high degree of confidence. The Applicant's cardiology consultant presenting at the July 2017 VRBPAC referred to ruling out a relative risk of at most 2;[23] the CDER guidance for therapeutic diabetes medications suggests using an upper bound of 1.3 in a post-marketing study to rule out an elevated risk.[51] In addition, problems with incomplete event ascertainment and loss to follow-up may be more pronounced in a post-marketing setting, leading to diminished ability to detect differences in treatment groups. Concerns were discussed with the Safety Working Group, including the CBER Director, on October 12, 2017.

APPENDIX A – ADVERSE EVENTS OF SPECIAL INTEREST, PRE-SPECIFIED IN DV2-HBV-23

Each subject will be assessed for these autoimmune, hypersensitivity, and inflammatory diseases during the trial. The following AESIs[a] will be evaluated and reported to FDA:

Gastrointestinal disorders
- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders
- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases
- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type 1
- Grave's or Basedow's disease

Musculoskeletal disorders
- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders
- Acute disseminated encephalomyelitis, including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Tolosa Hunt syndrome[b]
- Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)

- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse Myelitis

Skin disorders

- Alopecia areata
- Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis)
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-johnson syndrome
- Uveitis

[a] List provided to Dynavax Technologies by FDA on May 15, 2014
[b] Added by Dynavax

APPENDIX B – EXPERT CONSULTATIONS

The following consults appear below:

1. Four consults regarding the case of cavernous sinus syndrome/Tolosa-Hunt syndrome, reported in study DV2-HBV-16
2. Original CBER consult regarding AMI imbalance sent to one internal and two external cardiology consultants.
3. Three consults regarding the imbalance in cardiovascular events in study DV2-HBV-23.

Dr. Patricia Coyle, Neurology Department, Stony Brook Medicine

I have reviewed the provided data, including the January 23, 2013 memorandum, as well as the July 18, 2009 consultation regarding the Wegener's granulomatosis case.

In summary, I do feel this patient meets the criteria for Tolosa-Hunt syndrome (THS) as we currently apply it. These patients can have negative MRI scans. The clear-cut response to steroids is really highly suggestive, and not expected with cavernous sinus syndrome. The etiology of THS is not known for sure, but the presumption is that it is immune mediated. Certainly there is nonspecific inflammation pathologically, and excellent response to steroids, both of which support an etiologic term immune-mediated etiology. This etiologic term (immune mediate) seems more appropriate than autoimmune, which implies an auto-antigen target. THS is generally considered under orbital inflammatory diseases, and within the spectrum of idiopathic orbital inflammation.

Questions for the consultant

1. Based on the information provided, is this case consistent with THS?

   The most up-to-date diagnostic criteria for THS are from the 2004 International Headache Society. Diagnostic criteria are:

   a) One or more episodes of unilateral orbital pain persisting for weeks if untreated
   b) Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy
   c) Paresis coincides with pain onset, or follows within 2 weeks
   d) Pain and paresis resolve within 72 hours of adequate corticosteroids
   e) Other causes have been excluded by appropriate investigations

There has been debate about whether MRI inflammatory changes should be required for diagnosis. In one review of 124 cases, only 35% showed MRI inflammation or biopsy evidence of granuloma; 33% had normal neuroimaging; and 31% turned out to have a specific lesion with a secondary syndrome (Lamantia et al, 2006). In a series of 126 consecutive cavernous sinus syndrome patients, the most common cause (in 64%) turned out to be a tumor (Fernandez et al, 2007). However pain at onset of the syndrome, and cranial nerve III involvement, were independently associated with THS.

Although this patient never showed MRI evidence of cavernous sinus inflammation/granulomatous tissue, I believe they do meet all the diagnostic requirements: episodes of unilateral orbital pain; involvement of the third nerve; onset of diplopia within a short period of the left orbit pain (December 31, 2010 pain onset to early January 2011 intermittent diplopia onset, to January 31, 2011 persistent diplopia); excellent pain resolution with steroids (confirmed on multiple occasions); and other causes excluded. Cranial nerve III is most commonly affected in THS (85%), with 30% showing involvement of cranial nerve V (first division), as did this gentleman. There was no evidence for tumor, stroke, sarcoidosis, or infection. Therefore I do think this patient would qualify for THS, even though having a normal MRI is unusual. In a 2008 literature search that reviewed the diagnosis in 62 patients; 92.1% had a positive MRI which normalized after clinical resolution (Colnaghi et al, 2008).

2. Is there any overlap between THS and Wegener's granulomatosis?

Granulomatosis with polyangiitis (Wegener's granulomatosis), according to the 1990 American College of Rheumatology Criteria, requires two of four criteria: 1. Nasal or oral inflammation (painful or painless oral ulcers, or purulent/bloody nasal discharge). 2. Abnormal chest x-ray (nodules, fixed infiltrates, or cavities). 3. Urine microhematuria (>5 RBCs per HPF), or RBC casts in the urine sediment. 4. Granulomatous inflammation on biopsy in the arterial wall or perivascular/extravascular area around arteries or arterioles. This is a rare multisystem presumptive autoimmune disorder with necrotizing granulomatous inflammation and vasculitis involving small and medium sized blood vessels. It is an ANCA-associated vasculitis, with a predilection for the upper and lower respiratory tracts, and the kidney. Generally there are diffusely staining antibodies against cytoplasmic ANCA (C-ANCA) directed against serine proteinase 3 antigen.

Clearly THS is not Wegener's. However, there are limited forms of Wegener's relatively confined to the respiratory tract region. There has been speculation that THS may be a limited form of Wegener's (Montecucco et al, 1993; Thajeb et al, 2000). Patients described in this category were C-ANCA positive however. Wegener's was reported to involve the cavernous sinus, but this was associated with significant sinus disease (Fadil et al, 2007).

The pathology is similar but not identical. I believe the data does not strongly support true overlap. Clearly they are both inflammatory disorders, which can involve the cavernous sinus.

3. If you determine that this is a case of THS, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of THS in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.

Both THS and Wegener's are rare disorders. The annual incidence of Wegener's in the United States is estimated at 10 per million, while the incidence of THS is estimated at 1 per million. Therefore the likelihood of finding one case of each in 4,000 individuals over a year is extraordinarily unlikely, and does raise concern about a possible link to immune- mediated inflammatory diseases. Of note, the THS case was eight months after the last vaccination however.

4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegner's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.

As noted above, the link between Wegener's and THS is questionable. THS is not a limited Wegener's. That being said, both are likely immune mediated. Wegener's can rarely produce local involvement that mimics THS, and it would be difficult to rule out that there might not be some etiologic links promoting similar immune-mediated processes, given the relative rarity of both these disorders. However, it is clear that Wegener's and THS are not the same.

5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any, do you think the TLR-9 agonist adjuvant played?

There has been an ongoing but low level concern about the Hepatitis B vaccine and immune-mediated events. This was reviewed in the July 18, 2009 commentary, question 3.

The current test vaccine is using a unique adjuvant; there is very limited experience with it. The adjuvant clearly works by activating toll like receptor-9 (TLR-9). TLR-9 has been implicated in the pathogenesis of immune-mediated disease such as systemic lupus erythematosus. Therefore there is a concern that this particular vaccine and adjuvant could be involved. However, multiple autoimmune disorders are not being seen. The THS case, following the issue of the Wegener's case, is a clear concern. However, the data is not sufficient currently to prevent this vaccine development. In my opinion, they are two distinct disorders.

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?

THS is a diagnosis of exclusion. You need to rule out primary tumor, lymphoma or metastatic tumor; aneurysm; carotid cavernous sinus fistula; carotid dissection; cavernous sinus thrombosis; infection; sarcoidosis; diabetic cranial neuropathy; giant cell arteritis or vasculitis; I believe basically these were ruled out. The highly

suggestive clinical syndrome, along with the very clear steroid response, made me comfortable that this is the correct diagnosis.

7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in his case?

I do not see any clinical test or information that was missed to make a more definitive diagnosis. Biopsy is not indicated. I do not believe angiography or MR venogram were necessary. I do not understand why the diagnosis was changed to cavernous sinus syndrome, although of course that is technically correct (THS is a cavernous sinus syndrome).

8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

None additional. Individuals with a history of autoimmune disease or significant auto-antibody titers should not be entered. It may be worthwhile noting eosinophilia, to see if there is any relationship to predicting issues.

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Consultative Review and Evaluation of Clinical Data

Subject: Request for Neurology consultation regarding HEPLISAV (BLA 125428)

From: Devanand Jillapalli, MD (Reviewer) Devanand Jillapalli
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Division of Neurology Products
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Through: Russell Katz, M.D (Director) Russell G. Katz
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To: Lorie B. Smith, MD, MHS and Alexandra S. Worobec, MD
Medical Officers
Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review Hematology
Center for Biologics and Evaluation

Material Reviewed: Consult request, possible Tolosa-Hunt syndrome case summary and source documents, and relevant literature.

Date Received: January 2, 2013

Date Reviewed: February 28, 2013

The Division of Vaccines and Related Products Applications (DVRPA) from the Center for Biologics and Evaluation (CBER) has requested the Division of Neurology Products (DNP) to provide responses to the following questions:

1. Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?
2. Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis?
3. If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.
4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.
5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any do you think the TLR-9 agonist adjuvant played?

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?
7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?
8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

Background

In 2012, Dynavax Technologies Corporation (Sponsor) submitted a Biologics Licensing Application for HEPLISAV – a new vaccine for adult hepatitis B. The Agency issued a Complete Response letter on February 24, 2013 citing the need for further clinical evaluation and noting a concern that the vaccine's novel adjuvant may cause rare autoimmune events. In the consult request, DVRPA has provided the following background information.

HEPLISAV is comprised of recombinant hepatitis B surface antigen (rHBsAg) combined with a new cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant. The proposed indication for this new vaccine is for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age. Each 0.5 mL dose contains 20 mcg of rHBsAg and 3000 mcg of the 1018 ISS adjuvant. The proposed dosing regimen is two 0.5 mL doses administered 1 month apart.

There is currently no other licensed vaccine in the U.S. that contains this adjuvant. The mode of action of CpG ODNs is based on the concept that, whereas vertebral (self) DNA is usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences, which are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9). HEPLISAV is proposed to act by using an adjuvant that activates TLR9 which combined with HBsAg, leads to production of HBsAg-specific antibodies.

While TLR activation is critical for initiation of the innate and adaptive immune response to invading pathogens, the inappropriate activation of the innate immune system may, in principle, induce autoimmune responses and chronic inflammatory diseases. In light of the theoretical potential for TLR-agonist adjuvants, such as CpG, to induce or exacerbate autoimmune disease in humans, efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as anti-dsDNA, ANA, and ANCA, in individuals enrolled in studies of HEPLISAV.

Two randomized, controlled Phase 3 trials, study DV2-HBV-10 and DV2-HBV-16, compared the safety and immunogenicity of HEPLISAV to that of the active comparator, ENGERIX-B. ENGERIX-B is a licensed vaccine against hepatitis B comprised of recombinant antigen adsorbed to aluminum hydroxide. The Phase 3 trials were conducted in 4,864 subjects (HEPLISAV: N=3777, ENGERIX-B: N=1087) followed for adverse events and for serious adverse events for 28 weeks in study DV2-HBV-10 and 52 weeks in DV2-HBV-16. Additionally, there were 7 other supportive trials conducted in a total of 981 subjects

(HEPLSIAV: N=648, ENGERIX-B: N=333) followed for safety events for various time periods. The total safety database included 5845 subjects (HEPLISAV: N=4425, ENGERIX-B: N=1420). The results of the safety evaluation will be briefly summarized here.

Two deaths occurred in study DV2-HBV-16 – one each in HEPLISAV group (46 year old previously healthy male recipient died of a pulmonary embolus (b) (6) days after the second study injection) and ENGERIX-B group (64 year old male with multiple comorbidities died of cardiac arrest after having a myocardial infarction (b) (6) days after the second study injection). There was a numerical imbalance between the incidence of pulmonary embolus in HEPLISAV [5 (0.1%)] and ENGERIX-B recipients [0]. All five events occurred in individuals with underlying predisposition to thrombosis. Non-serious thrombotic events occurred with similar incidence between groups.

Because of the nature of the adjuvant, efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as ANA, anti-dsDNA, and ESR in individuals enrolled in studies of HEPLISAV. DVRPA review notes that there were no clinically significant differences in autoimmune laboratory parameters between groups.

A previously healthy HEPLISAV recipient from study DV2-HBV-10 developed granulomatosis with polyangiitis (Wegener's granulomatosis) in 2008. The clinical development program was placed on clinical hold because of this event. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) was consulted on 7/18/2009. In September 2009, the clinical hold was lifted allowing the Sponsor to resume Phase III studies with additional monitoring.

In addition to the healthy patient who developed granulomatosis with polyangiitis, another ENGERIX-B recipient with a history of mixed connective tissue disease from study DV2-HBV-10 developed p-ANCA positive vasculitis. Based on the occurrence of these two events, the Sponsor conducted additional retrospective evaluations of serum specimens from trial subjects, and further analyses of adverse events were performed in an attempt to assess possible cases of autoimmunity. A retrospective analysis of adverse events that required immunosuppressive therapy (excluding asthma exacerbations and those on immunosuppressive therapy at baseline) was performed. This analysis showed a case of possible Tolosa-Hunt syndrome which is of interest because of its potential vasculitic or other autoimmune etiology. Reports in the literature suggest that this condition could be a limited form or initial presentation of Wegener's granulomatosis, and ANCA testing is often negative in this possible limited form of Wegener's granulomatosis. Because of the possibility of the occurrence of what may be a second vaccine-related case of granulomatous inflammatory disease in HEPLISAV trial subjects, DVRPA seeks the consultant's opinion regarding whether this case fulfills the criteria for diagnosis of Tolosa-Hunt syndrome.

DNP Response
The following are DNP responses to each of the questions in the consult request.

1. Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?

Case Narrative: Subject #40-416 was a 69-year-old while male with no pertinent medical or surgical history other than recurrent rashes of uncertain etiology who received two HEPLISAV injections on 3/22/10 and 4/19/10 (and a saline placebo injection on 9/8/10). About 3 weeks after the first study injection, he experienced pruritic erythematous rash on elbows bilaterally which resolved with a course of topical steroids, and about 3 months after the second study injection experienced recurrent bouts of osteoarthritis of the right hand treated with oral and intramuscular injections of steroids. Subject reportedly developed "amblyopia" about 6 months after the second study injection which "failed to improve with corrective lenses". Severe headaches began more than 7 months after the second study injection. Three weeks after onset of these headaches, he sought evaluation in an emergency room for complaints of frontal headaches on the left. CT of the head and maxillofacial region showed minimal mucosal thickening of the ethmoid air cells bilaterally. He was discharged on antibiotics and hydrocodone for pain, but returned three days later with a left sided headache, pain around the left eye and numbness of the left forehead. He was given methylprednisolone in the ER (pain resolved while in the ER) but it is not clear if he was given a course of steroids. Shortly thereafter (more than 8 months after the second study injection), he was evaluated by an ophthalmologist for intermittent diplopia associated with headaches and was given a course of steroids. Symptoms significantly improved but headache returned after steroids were discontinued.

About one month after he was evaluated by the ophthalmologist (more than 9 months after the second study injection), he was hospitalized (or (b) (6) for severe headache on the left, persistent double vision x 5 days, numbness on the left side of the face (forehead to upper lip), worsening of left eye droop, and worsening of vision. Physical examination showed that he was afebrile with ptosis on the left, slight adduction deficit on the left eye with deviation to the left on primary position, pupils equally reactive to light and left V1 deficit. Consulting ophthalmologist at admission noted that there was no jaw claudication or scalp tenderness, that "headache improved tremendously the next day" after starting oral steroids in the previous month and in addition, noted visual acuity of 20/50 left eye, severe ptosis with no edema or redness, abducens palsy on the left, and essentially unremarkable fundus. The ophthalmologist concluded that there was a high suspicion for cavernous sinus syndrome (inflammatory/tumor /vascular), likely inflammatory etiology considering tremendous improvement of symptoms with systemic steroids in the previous month. Prednisone 60 mg daily was initiated at admission. MRI of brain (with contrast) and CT angiography of the head were unremarkable. MRA of the circle of Willis was normal. Cerebrospinal fluid analyses (CSF) were normal; CSF bacterial culture were negative and VDRL non-reactive. The Attending Physician noted on 2/5/11 that imaging did not reveal evidence of cavernous sinus inflammation and the plan was to continue steroid and obtain MRI of orbits to rule out Tolosa-Hunt syndrome. MRI of the orbits with contrast showed normal globes and retrobulbar soft tissue, ophthalmologic veins, optic nerve and chiasm, and no abnormal signal or enhancement. Chest X-ray showed blunting of the left costophrenic angle and otherwise was normal. Serologic workup including TSH, angiotensin converting enzyme, erythrocyte sedimentation rate (16 mm), random blood glucose, c-reactive protein and ANA all of which were normal. Antibodies to myeloperoxidase, serine protease 3, Smith antigen, SSA, SSB and RNP were not detected. Headache, left eye pain and numbness of the face had resolved 3 days later, and he was discharged on oral prednisone with a diagnosis of Tolosa-Hunt

syndrome. About 6 weeks after discharge, physical examination was noted to be normal with the exception of a faint blanching rash limited to the upper extremities. Subsequent discussions between the sponsor and attending neurologist took place, and via an email (4/1/11), the neurologist changed the diagnosis from Tolosa-Hunt syndrome to cavernous sinus syndrome, noting that "…. he was diagnosed of Tolosa-Hunt syndrome. His workup was negative. So I think the more appropriate diagnosis in this context would be cavernous sinus syndrome."

DNP response:
Diagnosis of neurological disorders typically begins with anatomic localization of the lesion followed by generation of differential diagnoses taking into consideration the potential pathological processes and etiologies as suggested by the clinical history/features and site of the lesion. The diagnosis of the above case will be discussed in that order.

The important clinical signs that this patient exhibited at hospital admission were severe ptosis (sympathetic fiber involvement from cavernous plexus), cranial 3, 5 (ophthalmologic branch) and 6 neuropathies, and to a lesser extent optic neuropathy, all on the left, localizing the anatomic site of the lesion to the superior orbital fissure, apex and/or the anterior cavernous sinus. The pertinent clinical features were those of severe headaches on the left for about 2 months which were "improved tremendously the next day" to oral steroids and which recurred after cessation of steroid therapy. Thus, the clinical presentation was that of a subacute painful unilateral ophthalmoplegia which is usually traceable to one of the several potential underlying pathophysiological processes – aneurysm, tumor or inflammatory/ granulomatous process, in the anterior portion of the cavernous sinus or the adjacent superior orbital fissure[1].

After reasonably excluding intracranial aneurysms or tumor in or near the vicinity of the site of interest by MRI of the brain (with contrast), CT angiography and MRA of the brain (these images which were provided by CBER on a DVD disc were also reviewed), an idiopathic inflammatory/granulomatous condition, termed Tolosa-Hunt syndrome[1], is most likely present. Some authorities on the subject state that the inflammatory changes in Tolosa-Hunt syndrome are limited to the superior orbital fissure[1]; however, others think that the inflammation is in the cavernous sinus[2-4], while still others opine that it affects the cavernous sinus, superior orbital fissure and the apex of the orbit[5-7]. The superior orbital fissure and the anterior cavernous sinus are contiguous structures; therefore, it is not surprising, that the inflammation in Tolosa-Hunt syndrome can localize to the superior orbital fissure and/or the anterior cavernous sinus. Inflammatory changes in any of these contiguous structures can result in similar clinical presentation and cranial deficits. It is for this reason, perhaps, that there is confusion in nosology: Tolosa-Hunt syndrome is sometimes used synonymously with cavernous sinus syndrome when inflammation is thought to be the underlying process (we prefer to use the term 'Tolosa-Hunt syndrome'). Of note, cavernous sinus syndrome can also result from other pathophysiological processes such as trauma or neoplastic invasion[1], carotid-cavernous fistulas, compression from an intracavernous internal artery aneurysm, thrombophlebitis, or rare but life-threatening infections (bacterial, or fungal – aspergillosis, mucormycosis in diabetic or immunosuppressed patients)[2-3]. In this patient, the clinical features, investigations and clinical response as described above have reasonably excluded these alternate pathological processes that can potentially affect the cavernous sinus.

A marked response with reduction in pain and improved ophthalmoplegia in one or two days of treatment with corticosteroids is confirmatory of the diagnosis of Tolosa-Hunt syndrome[1]. In this patient, the dramatic improvement to oral steroids, followed by relapse after cessation of steroid therapy, and during hospitalization one month later, resolution of headache, left eye pain and numbness of the face and improvement of ophthalmoplegia within a few days after starting high prednisone (60 mg/day) is strongly supportive of the diagnosis of Tolosa-Hunt syndrome. Other inflammatory conditions such as orbital pseudotumor (inflammatory enlargement of the extraocular muscles often accompanied by injection of the conjunctiva and lid and proptosis), sarcoidosis, lymphomatous infiltration, temporal arteritis or tumors of the parasellar region can also respond to steroid therapy. In this patient, normal MRI of the orbits and brain (both with contrast), chest X-ray, normal angiotensin converting enzyme levels, normal erythrocyte sedimentation rate, unremarkable cerebrospinal fluid analyses, the presenting clinical features including the absence of symptoms of jaw claudication or scalp tenderness, reasonably exclude these alternate etiologies.

The International Classification of Headache Disorders (ICHD)-II criteria for Tolosa-Hunt syndrome (see below) are essentially clinical and do not mandate the demonstration of granulomas by MRI or biopsy[8]. MRI of brain/orbits is essential to exclude alternate diagnoses but the demonstration of granulomas by MRI is not necessary for diagnosis of Tolosa-Hunt syndrome. Several authors argue that MRI demonstration of granulomas should play a pivotal role in the diagnosis because it was positive in 92.1% of cases (based on retrospective review of literature) and normalized after treatment[5-6]. Despite these assertions, the diagnosis of Tolosa-Hunt syndrome remains largely clinical, relying on clinical presentation, response to steroids and exclusion of alternate diagnoses[1,2,8,9]. Biopsy is considered only in patients with rapidly progressive neurological impairment, high risk for malignant diseases, lack of response to steroids or other unusual findings in MRI[9]. Applying the ICHD-II criteria further supports the diagnosis of Tolosa-Hunt syndrome in this patient.

Diagnostic criteria:

A. One or more episodes of unilateral orbital pain persisting for weeks if untreated
B. Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granulomas by MRI or biopsy
C. Paresis coincides with the onset of pain or follows it within 2 weeks
D. Pain and paresis resolve within 72 h when treated adequately with corticosteroids
E. Other causes have been excluded by appropriate investigations[1]

Note:

1. Other causes of painful ophthalmoplegia include tumours, vasculitis, basal meningitis, sarcoid, diabetes mellitus and ophthalmoplegic 'migraine'.

Comments:

Some reported cases of Tolosa–Hunt syndrome had additional involvement of the trigeminal nerve (commonly the first division) or optic, facial or acoustic nerves. Sympathetic innervation of the pupil is occasionally affected.

The syndrome has been caused by granulomatous material in the cavernous sinus, superior orbital fissure or orbit in some biopsied cases.

Careful follow-up is required to exclude other possible causes of painful ophthalmoplegia.

2. Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis?

In 1954, Tolosa described a male patient who died a few days after an exploratory surgery of the sella turcica for left retro-orbital pain and ophthalmoplegia; the histopathological findings at post-mortem showed granulomatous tissue wrapped around the intracavernous portion of the carotid artery and without endoarteritic or mesoarteritic lesions[10]. In 1961, Hunt described a new syndrome on the basis of six patients with similar symptoms that improved with corticosteroids, and despite the lack of histopathological data postulated that this syndrome was caused by an inflammation of the cavernous sinus[4]. Biopsy is not routinely obtained in patients with Tolosa-Hunt syndrome, and consequentially, there is little data on histopathology[9,11].

Wegener's granulomatosis has a special predilection for orbital tissue, and eye involvement (in 52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions leading to proptosis[12-13]. Some authors have reported cases of patients with Tolosa-Hunt syndrome with the presence of c-ANCA but without obvious systemic vasculitis, and another case with negative ANCA, and argue that it could be consistent with a localized form of Wegener's granulomatosis[14-15]. Others have reported a case of a woman with multiple cranial deficits related to a mass lesion in the orbit and cavernous sinus, epidural mass with thickened dura and positive c-ANCA and favorable response to steroids and another immunosuppressant[16].

Several authors consider Wegener's granulomatosis as a secondary cause or one of the clinical differential diagnoses of steroid-responsive painful ophthalmoplegia[5,9], implying that Tolosa-Hunt syndrome and Wegener's granulomatosis are separate entities.

We are uncertain whether Tolosa-Hunt syndrome is a limited form of Wegener's granulomatosis, or an independent entity with or without an overlap between it and Wegener's granulomatosis. You may wish to consult others with expertise in autoimmune disorders in this regard.

3. If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.

Iaconetta et al estimate the incidence of Tolosa-Hunt syndrome to be approximately one to two cases per million but it is not clear on what basis this estimate was made as they do not cite supporting epidemiological data[7]. The lack of epidemiological data makes it difficult to estimate the incidence of Tolosa-Hunt syndrome reliably. Given this limitation, a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals appears to be higher than what would be expected to occur spontaneously.

You may wish to consult others with expertise in autoimmune disorders with regard to the likelihood of identifying a case of Wegener's granulomatosis in this database.

4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.

Please our response to Question 2.

5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any, do you think the TLR-9 agonist adjuvant played?

We are unable to provide a response to this question as we lack the necessary expertise.

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?

No. As discussed in our response to Question 1, we believe that this case is consistent with Tolosa-Hunt syndrome.

7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?

Please our response to Question 1.

8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

There are no subject characteristics or risk factors that we are aware of that might predispose subjects to developing Tolosa-Hunt syndrome. We do not have any particular recommendations for additional safety monitoring for clinical trials involving vaccines with CpG adjuvant.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date: May 6, 2013

/s/

From: Michael C. Sneller, M.D.,
Laboratory of Immunoregulation, NIAID/NIH

To: Lorie B. Smith, M.D., M.H.S., Division of Vaccines and Related Products Applications,Office of Vaccines Research and Review Center for Biologics and Evaluation

Subject: Request for consultation regarding HEPLISAV (rHBsAg-1018 ISS)

I have reviewed the material (summary documents, neurologic consultant notes, laboratory results, and radiology reports) you sent me as part of the above consultation request. Below are my responses to the questions posed in the Consultation Request.

Questions for the consultant

1. **Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?**

   I am not an expert in Tolosa-Hunt syndrome, but based on the information provided, this patient's illness sounds most consistent with that diagnosis.

2. **Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis**?

   With regards to a possible association between Tolosa-Hunt syndrome and Granulomatous with polyangiitis (GPA; formerly Wegener's granulomatosis), I do not think there is convincing evidence that the two disorders are in anyway associated with regards to clinical-pathologic features or pathogenesis. I was only able to find 2 reports in the English language literature that suggest a possible association with GPA and Tolsa-Hunt. The report by Montecucco et. al (reference 14 in your summary document) describes 2 patients with (what seems to me) typical Tolosa-

Hunt syndrome. Both patients are reported to have c-ANCA detected by indirect immunofluorescence (not confirmed by anti-Pr3 EIA-this assay was not available in 1992). Relying on immunofluorescence (IF) testing alone for c-ANCA is not adequate for diagnostic purposes, as there are false positives, especially in laboratories that are not experienced in performing IF assays. Testing for c-ANCA by IF has largely been abandoned and has been replaced by anti-Pr3 EIAs, which are less susceptible to observe interpretation. Testing for c-ANCA (by any method) has a high positive predictive value for the diagnosis of GPA only in patients with a clinical syndrome suggestive of GPA (i.e. sinusitis, glomerulonephritis, pulmonary nodules and/or infiltrates where infection has been excluded). In patients who do not have a clinical syndrome suggestive of GPA (such as the patients in the report by Montecucco et al.) the positive predictive value of c-ANCA for the diagnosis of GPA is poor. Contrary to popular practice, ANCA is not a good screening test for GPA or any kind of vasculitis. This was demonstrated many years ago in a paper from Duke (see Rao et. al Lancet 346:926-931, 1995). Thus, the finding of a positive c-ANCA (by IF only), in 2 patients with Tolosa-Hunt syndrome who do not have clinical features suggestive of GPA, is most likely a false positive IF and does not constitute evidence for a pathophysiologic association between the two disorders.

The second paper by Thajeb (reference 13) describes a patient who actually had multiple features suggestive of GPA. In addition to painful ophthalmoplegia, this patient had otitis media with hearing loss that was refractory to surgical/antibiotic therapy, sinusitis, mastoiditis, mononeuritis multiplex and pachymenigitis (MRI showing meningeal enhancement, CSF pleocytosis with elevated protein). These are all known manifestations of GPA and occasionally can be the presenting features. The patient in this report had a positive c-ANCA and likely had GPA, not Tolosa-Hunt syndrome.

3. **If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.**

I'm not sure all the patients in your database can be classified as "otherwise healthy". The patient in this report had multiple other health problems including presbyopia, bilateral hearing deficit, seasonal allergic rhinitis, hypertension, gastroesophageal reflux disease, esophageal ulcer,

benign prostatic hyperplasia, osteoarthritis. That being said, I would think that finding single cases of 2 rare, unrelated diseases out of 4,000 individuals could occur by chance alone.

4. **If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.**

   I do not think GPA and Toloso-Hunt syndrome are related (see response to #2)

5. **In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any do you think the TLR-9 agonist adjuvant played?**

   I 'm not an expert in TLR-9 immunobiology, but it seems to me that a localized injection of a small amount of TLR-9 agonist would be unlikely to produce organ specific autoimmunity at a distant site (Tolosa-Hunt) or a systemic autoimmune disease (GPA).

6. **Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?**
   Not that I can think of.

7. **What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?**
   Nothing I can suggest based at this point

8. **What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?**
   None I can think of.

Walter Reed National Military Medical Center

Dr. Eric D Weber, MC, MAJ, USA

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May 8, 2013

To Whom it May Concern,

I have reviewed the consultation regarding the HEPLISAV vaccine and its possible linkage to one case of Tolosa-Hunt syndrome (THS). Based on the information provided, I believe this case is consistent with Tolosa-Hunt. I understand that the diagnosis was changed to "cavernous sinus syndrome," (CSS) but this is a very vague description under which THS is just one of the causes. Since this patient was very responsive to steroids, this implies that the cause of his CSS had to be inflammatory; one of the more common causes of inflammatory CSS is THS or granulomatous disease. Unfortunately, the MRI was non-diagnostic for this, and there is no tissue biopsy to give a definitive diagnosis. Therefore, this case could also be the result of many other causes of cavernous sinus inflammation, to include pseudotumor, sarcoidosis, or TB. As best I can tell, these entities were worked up and there is no evidence that would suggest any of those as possible causes, but nothing is 100%.

There can be some overlap between THS and Wegener's granulomatosis. However, I would expect more orbital changes on his MRI or CT, and potentially more paranasal sinus disease. Furthermore, I believe the lab workup was entirely normal, which is not consistent with Wegener's. In addition, there were no systemic findings consistent with Wegener's to include arthritis, skin, nervous system or renal involvement. With that being said, there is no way to link a case of Wegener's with a case of THS, other than to say both are inflammatory and both are granulomatous in nature.

There is no way to link this case to the vaccine. The prevalence of Wegener's is approximately 3 per 100,000 with undetermined incidence, while THS carries an incidence of 1 case per million per year. Based on this study's small numbers, it would be highly unlikely to see either in your cohort of approximately 4000 patients. While it is theoretically possible for this vaccine with the TLR-9 antagonist to incite some forms of inflammation, I have no way of linking it definitively to these cases of inflammation. I think the only way to do this would be via a biopsy of the cavernous sinus that demonstrated some deposition of this recombinant protein.

Walter Reed
National Military
Medical Center

In conclusion, I cannot definitively or even remotely link this case of cavernous sinus disease with your vaccine. In the future, I recommend monitoring all patients for any signs of granulomatous disease, but this is a very broad category and requires surveillance of all major organ systems.

Please contact my office with any questions or concerns.

Sincerely,

/s/

Eric D. Weber, MD
MAJ, MC, USA
Pediatrics, Neuro-ophthalmology & Orbit
Associate Program Director
Ophthalmology Service
Walter Reed National Military Medical Center

Memorandum
Date: April 5, 2017

From: Darcie Everett, M.D., M.P.H., Medical Officer, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research
Subject: Request for consultation regarding HEPLISAV (rHBsAg-1018 ISS)

In 2012, Dynavax Technologies Corporation (Applicant) submitted a Biologics License Application (BLA) for Heplisav (125428/0) – a new vaccine for prevention of hepatitis B infections in adults 18 - 70 years of age. On November 15, 2012, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) voted 8 to 5 that the safety data available for Heplisav was not adequate to support licensure due to insufficient numbers in the safety database for a novel adjuvant. The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration subsequently issued a Complete Response (CR) letter, citing the need for further clinical safety evaluations to obtain a larger safety database.

In response, the Applicant conducted DV2-HBV-23, a randomized safety study in 8,300 subjects, comparing Heplisav (5500 subjects) to Engerix-B (2750 subjects). The results of this trial were submitted to the BLA March 16, 2016. A numerical imbalance in the unsolicited adverse event (MedDRA preferred term) acute myocardial infarction (AMI) was observed in this trial (14 subjects who received Heplisav, 1 subject who received Engerix-B). This imbalance had not been noted in previous trials. CBER sent an information request (IR) on September 9, 2016, which included a request for any additional analyses regarding the imbalance in AMI the Applicant had conducted. The Applicant responded via several submissions to the BLA from September 26, 2016 – October 11, 2016. CBER issued another CR letter on November 10, 2016, which included the items in the September 9th IR, as well as several additional items. The Applicant submitted the response to the CR on February 7, 2017, which is currently under review. CBER is seeking advice on a comprehensive evaluation of the imbalance in AMI to support our evaluation of the risk-benefit profile of the vaccine.

Product

Heplisav is a vaccine comprised of recombinant hepatitis B surface antigen (rHBsAg) combined with 1018 immunostimulatory sequence (ISS), a synthetic unmethylated cytosine phosphoguanine (CpG) enriched phosphorothioate oligodeoxynucleotide (ODN) adjuvant. Currently, there are no other licensed vaccines in the U.S. containing this adjuvant. The proposed indication is for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age. Each 0.5 mL dose contains 20 mcg of rHBsAg and 3000 mcg of the 1018 ISS adjuvant. The proposed dosing regimen is two 0.5 mL doses administered one month apart. Although safe and effective hepatitis B vaccines have been available for years, the Applicant notes the potential for improved immunologic response in certain subsets of individuals and the requirement for fewer doses (two vs. three doses) over a shorter period of time (one vs. six months), compared to available products, as the rationale for Heplisav's development.

Heplisav is proposed to act by using an adjuvant that activates toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells (pDCs), which combined with HBsAg, leads to production of HBsAg-specific antibodies. Protein antigens administered by intramuscular (IM) injection are thought to distribute from the site of injection via lymphatic channels to the draining lymph node, where the antigens are processed into peptides and presented by antigen-presenting cells. The mode of action of the CpG ODN adjuvant is based on the concept that, whereas guanine residues of vertebral (self) DNA are usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences, which are recognized as foreign by the innate immune system. Based on studies with CpG-ODNs in cultured human peripheral blood mononuclear cells,[1, 2] the Applicant attributes activity of Heplisav to the following: (1) activation of plasmacytoid dendritic cells (pDCs) through TLR9 receptor recognition of the unmethylated CpG sequence, (2) conversion of pDCs into dendritic cells that present the processed HBsAg component of Heplisav to CD4+ T cells, and (3) promotion of Th1 T-cell differentiation through the production of IFN-α and IL-12. The Applicant asserts that this activation results in an enhanced and sustained antibody response to HBsAg, likely due to generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory cells.

As per the Applicant, pharmacokinetics of phosphorothioate ODNs are similar across the molecular class. Phosphorothioate ODNs are synthetic molecules in which the natural phosophodiester bonds of DNA are replaced by synthetic thioether linkages to increase stability and slow metabolism. Following intravenous or subcutaneous administration, phosphorothioate ODNs are rapidly absorbed and detected in the plasma. They bind nonspecifically and reversibly to plasma proteins. Distribution from the plasma into tissues is rapid. Based upon observations in rodents and primates, phosphorothioate ODNs primarily distribute into kidney, liver, lymph nodes, spleen, adipose tissue and bone marrow. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow (measured in days to weeks) because the phosphorothioate backbone resists degradation. Small metabolites are filtered through the glomerulus and excreted in the urine. Phosphorothioate ODNs have minimal distribution to heart, lung, and skeletal muscle and do not cross the blood-brain barrier.[3, 4, 5]

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2 Krieg, A. M., A. K. Yi, S. Matson, T. J. Waldschmidt, G. A. Bishop, R. Teasdale, G. A. Koretzky and D. M. Klinman (1995). "CpG motifs in bacterial DNA trigger direct B-cell activation." Nature 374(6522): 546-549.
3 Geary RS, et. al. Pharmacokinetics of a tumor necrosis factor-alpha phosphorothioate 2'-O-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos, 2003; 31(11): 1419-1428.
4 Noll BO, et. al. Biodistribution and metabolism of immunostimulatory oligodeoxynucleotide CPG 7909 in mouse and rat tissues following subcutaneous administration. Biochem Pharmacol, 2005; 69(6): 981-991.
5 Geary RS. Antisense oligonucleotide pharmacokinetics and metabolism. Expert Opin Drug Metab Toxicol, 2009; 5(4): 381-391.

Pre-clinical Trials

Preclinical studies of 1018 ISS alone and of the antigen and adjuvant combination were conducted. The main treatment-related findings of repeat dose toxicity studies of 1018 ISS alone in mice, rats, and cynomolgus monkeys were non-degenerative and reversible inflammatory changes at the injection-sites and in key target organs, consistent with the immunostimulatory activity of 1018 ISS adjuvant and its adjuvant class effects. These effects were more pronounced in rats than monkeys. Cardiomyopathy was observed in rats at a similar incidence between treatment and control groups and, given this established background finding in this animal, was assessed as not related to test article. A repeat dose toxicity study of Heplisav was conducted in mice. Epicardial mineralization was observed microscopically in animals receiving antigen with high dose adjuvant (acute phase: 50%, recovery phase: 30%) and in animals receiving the antigen alone (acute phase: 15%, recovery phase: 20%). Animals in the control group, antigen/low-dose adjuvant and antigen/mid-dose adjuvant did not show epicardial mineralization. Since epicardial mineralization is a common spontaneous lesion in mice, this finding was not determined to be treatment related. No significant toxicity was observed in the pre-clinical studies and all effects were thought to reflect the expected immunostimulatory properties of the vaccine.

Clinical Trials in the original BLA submission

Data from two multi-center, randomized, controlled, Phase 3 trials were included in the initial BLA submission: DV2-HBV-10, conducted in Canada and Germany, and HBV-16, conducted in the US and Canada. These studies compared the safety and immunogenicity of Heplisav, administered Weeks 0 and 4 (placebo administered Week 24) to that of the active comparator, Engerix-B. Engerix-B is a licensed vaccine against hepatitis B comprised of recombinant antigen adsorbed to aluminum hydroxide and administered at Week 0, 4, and 24. The Phase 3 trials were conducted in healthy subjects, age 11 through 55 years in DV2-HBV-10 and age 40 through 70 years in DV2-HBV-16, with no history or serologic evidence of infection with or vaccination for hepatitis B. A total of 4,864 adult subjects (Heplisav: N=3,778, Engerix-B: N=1,086) were enrolled and vaccinated in the pivotal studies. Thirteen subjects younger than 18 years of age were enrolled in DV2-HBV-10, but had no adverse events (AEs) relevant to this consult and are not further discussed. Subjects were followed for AEs for 28 weeks (from first injection) in both studies, for serious adverse events (SAEs) for 28 weeks in DV2-HBV-10, and for SAEs, adverse events of special interest, and potential autoimmune events for 52 weeks in DV2-HBV-16. Additionally, there were seven other supportive trials conducted in a total of 965 subjects (Heplisav: N=632, Engerix-B: N=333) followed for safety events for various time periods. The safety database of these nine trials included 5,829 subjects (Heplisav: N=4,410, Engerix-B: N=1,419). The results of the safety evaluation of these studies performed for the first BLA review are briefly summarized here.

The overall incidence of non-serious adverse events was similar between treatment groups (Heplisav 58.1%, Engerix-B 61.2%). Solicited adverse events of fever, malaise, headache,

fatigue, injection site swelling, and injection site pain occurred with similar incidence between treatment groups. More subjects receiving Heplisav reported redness at the injection site (3.5% vs. 1.0%) than did subjects receiving Engerix-B. Non-fatal SAEs were reported by 2.7% of Heplisav and 3.7% of Engerix-B recipients. Two subjects who received Heplisav and reported no history of autoimmune disease had diagnosed or suspected rare immune-mediated events following vaccination.

Two deaths occurred in study DV2-HBV-16. One 64-year-old male Engerix-B recipient (92-638) with hypertension died of cardiac arrest after having a myocardial infarction (b) (6) days after the second study injection (preferred term "cardiac failure"). One 46-year-old previously healthy male Heplisav recipient (22-003) died of a pulmonary embolus (b) (6) days after the second study injection. In the total safety database, at the time of the initial BLA submission, there was a numerical imbalance between the incidence of pulmonary embolus in Heplisav and Engerix-B recipients at 5 (0.1%) and 0, respectively, including the fatal event. Four of the five events occurred in individuals with an underlying predisposition to thrombosis; there was no noted predisposition in the subject with the fatal pulmonary embolism. SAEs of deep vein thrombosis and non-serious thrombotic events occurred with similar incidence between groups. Three additional subjects had non-fatal myocardial infarctions reported in DV2-HBV-16, two who received Heplisav and one who received Engerix-B. In DV2-HBV-10, no deaths, myocardial infarctions, or events of stroke were reported during the 28-week study period.

Table 1 presents a summary of the major cardiovascular events identified in studies of Heplisav submitted in the initial BLA. In addition to the events of AMI identified in Study DV2-HBV-16, there were two events, one in each treatment group, of myocardial infarction that were identified in the supportive studies DV2-HBV-04 and -05. Both studies were double-blind, randomized trials conducted in Asia that enrolled adults 40 – 70 years of age, randomized 1:1 to receive an earlier formulation of Heplisav (same dose of antigen and adjuvant) at Weeks 0, 8, and 24 or Engerix-B at Weeks 0, 4, and 24. In both studies, SAEs were collected through Week 50.

Table 1. Summary of cardiac deaths and myocardial infarction reported in Heplisav studies in the initial BLA submission, Safety Populations, DV2-HBV-0001, -02, -03, -04, -05, -08, -10, -14, and -16

Study	Subject #	Age	Sex	MedDRA Preferred Term	Study Day	Last Active Dose	Day of event relative to most recent active dose*
Heplisav							
DV2-HBV-16	22-003	45	M	Pulmonary embolism†	75	2	(b) (6)
DV2-HBV-16	41-335	58	M	Acute myocardial infarction	22	1	22
DV2-HBV-16	20-610	63	F	Acute myocardial infarction	44	2	15
DV2-HBV-05§	010	52	M	Acute myocardial infarction	275	3	121
Engerix-B							
DV2-HBV-16	92-638	64	M	Cardiac failure†‡	73	2	(b) (6)
DV2-HBV-16	29-614	60	M	Acute myocardial infarction	39	2	11

Study	Subject #	Age	Sex	MedDRA Preferred Term	Study Day	Last Active Dose	Day of event relative to most recent active dose*
				and Unstable angina			
DV2-HBV-04§	11-009	43	F	Unstable angina	182	3	14

Source: Reviewer generated summary based upon 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety (Attachment 5, and 125428/0.42, Module 5.3.5.3, dataset ADAE for the integrated studies
* Day 1 is day of administration. An event start day relative to the most recent dose of x is x-1 days following the most recent dose.
§ Study utilized a previous formulation of Heplisav
† Fatal event
‡ Following a myocardial infarction

Study DV2-HBV-23

The Applicant conducted a safety study, DV2-HBV-23, to expand the total safety database in response to concerns expressed at VRBPAC and by CBER reviewers. The study was a Phase 3, randomized, controlled, double-blind trial comparing the safety and immunogenicity of Heplisav (Weeks 0 and 4, placebo Week 24) to that of the active comparator, Engerix-B (Weeks 0, 4, and 24). In addition to the primary objective of evaluating the safety of Heplisav, the Applicant expanded the study objectives to include evaluation of immune responses in subjects with Type 2 diabetes, a sizable subset of enrolled participants. Subjects were 18-70 years of age, with no history or serologic evidence of infection with or vaccination for hepatitis B, and no history of autoimmune disease. The trial enrolled 8,368 subjects (Heplisav: N=5,587, Engerix-B: N=2,781). Subjects were followed for medically attended events (MAEs), potential autoimmune events, adverse events of special interest, and serious adverse events for 56 weeks following the first dose of study vaccine (52 weeks following the final dose of Heplisav, 32 weeks following the final dose of Engerix-B). A Safety Evaluation and Adjudication Committee reviewed potential immune-mediated events. Monitoring for cardiovascular events was not a pre-specified outcome for this study and electrocardiography was not performed as part of the study.

Subjects enrolled and vaccinated in DV2-HBV-23 had a mean age of 50.4 years (range 18-71 years) and were 50.6% male; 71.4% White, and 25.8% Black; and 90.9% not Hispanic. Overall, SAEs were reported in 345 Heplisav subjects (6.2%) and 148 Engerix-B subjects (5.3%). Non-fatal SAEs were reported in 325 Heplisav subjects (5.8%) and 142 Engerix-B subjects (5.1%). MAEs were reported in approximately 46% in both study groups.

There were 32 deaths in study DV2-HBV-23, 25 in the Heplisav group (0.45%) and 7 in the Engerix-B (0.25%) (Table 2). None of the deaths were determined by the investigators to be related to study vaccination. Excluding deaths clearly due to illicit drug overdose or injury, an imbalance remains; 16 subjects in the Heplisav group (0.29%) and 4 subjects in the Engerix-B group (0.14%) were reported to have a non-overdose, non-injury death. Please see Appendix B for brief narratives of deaths reported in DV2-HBV-23 in the system organ class (SOC) of cardiac disorders and general disorders. Attachment 1 has detailed narratives provided by the Applicant.

Table 2. Fatal adverse events by treatment and system organ class, Safety Population, DV2-HBV-23

Subject #	Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
Heplisav						
Cardiac						
130084	50	M	Acute coronary syndrome*	1	7	(b) (6)
131091	69	M	Acute myocardial infarction*	2	57	
112311	57	M	Hypertensive heart disease	2	63	
132082	62	M	Hypertensive heart disease*	2	212	
138012	58	F	Hypertensive heart disease	2	225	
133120	70	F	Cardiac arrest	2	243	
122613	47	M	Myocardial infarction	2	287	
104152	55	F	Cardio-respiratory arrest	2	298	
General						
119318	61	F	Death – Unknown cause	2	59	
119290	51	F	Death – Unknown cause	2	354	
Hepatobiliary						
107176	68	M	Hepatic cirrhosis	2	27	
Infectious						
106407	56	M	Hepatitis C	2	35	
Injury and Poisoning or Social circumstances						
120406	58	F	Victim of homicide†	1	1	
122628	49	M	Toxicity to various agents†	2	3	
101017	38	M	Toxicity to various agents†	2	36	
123071	62	M	Overdose†	2	88	
138246	44	M	Toxicity to various agents†	2	159	
122188	49	M	Toxicity to various agents†	2	160	
119153	42	F	Gunshot wound†	2	283	
138160	49	M	Accident†	2	286	
Neoplasm						
125113	49	M	Lung cancer metastatic	2	244	
125139	43	F	Small cell lung cancer metastatic	2	300	
Nervous system						
125045	46	F	Hypoxic-ischemic encephalopathy†	2	191	
Respiratory						
131049	67	M	Acute respiratory failure	2	15‡	
121090	61	M	Acute respiratory distress syndrome§	2	120	
Engerix-B						
Cardiac						
135070	52	M	Myocardial infarction	1	12	
119175	48	M	Hypertensive heart disease§	3	27	
130392	69	M	Cardio-respiratory arrest	3	88	
Injury and Poisoning						
130269	44	M	Craniocerebral injury†	1	17	
122769	55	M	Toxicity to various agents†	2	99	
117008	33	F	Head injury†	3	162	
Neoplasm						
130252	67	M	Pancreatic carcinoma metastatic	3	179	

Source: Adapted from STN 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 12-3, p. 96
* Subject found dead. No autopsy performed.
† Events clearly due to overdose or injury.

‡ Initial event of COPD exacerbation leading to hospitalization and tracheostomy, which led to pneumonia and acute respiratory failure, began six days following Dose 2.
§ Alcohol and drugs contributed.

While rates of MAEs (including SAEs) in the SOC of cardiac disorders were similar between treatment groups (1.88% Heplisav, 1.62% Engerix-B), rates of cardiac SAEs were more frequent in the Heplisav group compared to the Engerix-B group (0.9% Heplisav, 0.5% Engerix-B). This imbalance was most notable in reports of the SAE of acute myocardial infarction (AMI) in 14 subjects in the Heplisav group (0.25%) and 1 subject in the Engerix-B group (0.04%). An imbalance in the MAEs, but not SAEs, of atrial fibrillation was also noted, with reports occurring more frequently in the Heplisav group. No differences between study groups were noted in pulmonary embolism or other venous thromboembolic events (0.21% Heplisav, 0.25% Engerix-B). An overview of all cardiac SAEs is shown in the table below.

Table 3. Number and proportion of subjects with treatment-emergent serious adverse events in the system organ class of cardiac disorders by treatment group, Safety Population, DV2-HBV-23

MedDRA Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	14 (0.25)	1 (0.04)
Angina pectoris	2 (0.04)	1 (0.04)
Angina unstable	1 (0.02)	0
Atrial fibrillation	6 (0.11)	3 (0.11)
Atrial flutter	2 (0.04)	1 (0.04)
Bradycardia	2 (0.04)	0
Cardiac arrest	3 (0.05)	0
Cardiac failure	4 (0.04)	0
Cardiac failure acute	1 (0.02)	0
Cardiac failure congestive	9 (0.11)	3 (0.11)
Cardiac ventricular thrombosis	1 (0.02)	1 (0.04)
Cardiogenic shock	1 (0.02)	0
Cardiomyopathy	0	1 (0.04)
Cardio-respiratory arrest	1 (0.02)	1 (0.04)
Coronary artery disease	6 (0.11)	2 (0.07)
Coronary artery occlusion	1 (0.02)	1 (0.04)
Coronary artery stenosis	2 (0.04)	0
Hypertensive heart disease	4 (0.07)	1 (0.04)
Myocardial infarction	2 (0.04)	1 (0.04)
Myocardial ischemia	1 (0.02)	0
Pulseless electrical activity	1 (0.02)	0
Supraventricular tachycardia	1 (0.02)	0
Ventricular fibrillation	1 (0.02)	0
Ventricular tachycardia	2 (0.04)	0
Total Subjects with at least 1 Cardiac SAE	**51 (0.91)**	**15 (0.54)**

Source: Adapted from 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 12-16, p. 105.
N number of subjects in each treatment group
n number of subjects reporting event
Shaded rows are events in the MedDRA standard medical query narrow for myocardial infarction.

In order to identify other events of myocardial infarction that may have been reported without the preferred term of AMI, the Applicant has used the Medical Dictionary for Regulatory Activity (MedDRA) standard medical query (SMQ) narrow for myocardial infarction (MI). SAEs with a preferred term in this SMQ are shaded in Table 3. Nineteen subjects in the Heplisav group (0.34%) and three subjects in the Engerix-B group (0.11%) reported an SAE with one of the five preferred terms (PTs) identified in this search.

Brief narratives for the non-fatal events with a PT in the SMQ narrow for MI are presented in Appendix C and based upon narratives provided by the Applicant (Attachment 1). Narratives for all cardiac SAEs reported in DV2-HBV-23, as well as other adverse events, were submitted in response to the September 9, 2016 IR and are also contained in this document. The narratives for the SAEs with PTs not included in the SMQ narrow for MI are currently under review. With the exception of the subject with "unstable angina" (122-174) and a cardiac catheterization demonstrating no significant disease, the clinical reviewer considers the other events have some evidence of acute coronary ischemia or were fatal events determined by the investigator to be cardiac in nature.

There was one additional subject (105-059), a 54 year-old woman, who reported an SAE of AMI during the screening period prior to vaccination and who is not included in the table above. This subject was treated with balloon angioplasty, recovered, and received two doses of Heplisav beginning thirteen days after the event onset. The only other MAE she reported was pharyngitis.

There were three additional subjects who reported a non-serious MAEs in the SMQ narrow for MI who are not included in the table above. One Heplisav subject (128-042) reported an MAE of MI 112 days following the first injection of Heplisav of one day duration and coded as treatment-emergent in the datasets. In the Clinical Study Report (CSR), on page 106, the Applicant reports that this event was actually a history of MI and not an acute treatment-emergent event. Two events of troponin increased were reported in two subjects in the Engerix-B group in the setting of another SAE (urosepsis and diabetes mellitus inadequate control). Further information on these events was requested in the complete response letter dated November 10, 2016.

In summary, excluding the Heplisav subject who had no significant disease on cardiac catheterization, treatment-emergent SAEs of MI were reported in 18 Heplisav subjects (0.32%) and 3 Engerix-B subjects (0.11%). As per the statistical reviewer, the relative risk is 2.99 (95% Confidence Interval (CI) 0.96, 17.83). The Applicant does not provide a statistical test of the difference in frequency of MI as determined by the SMQ in Study DV2-HBV-23 alone, but does provide a 2-tail Fisher Exact test, unadjusted for multiplicity, for the difference in cardiac SAEs in DV2-HBV-23 ($p = 0.07$).

The Applicant addressed the imbalance in AMI noted in DV2-HBV-23 in the March 2016 BLA submission in the DV2-HBV-23 CSR (Attachment 2, pp.104-106) and evaluated it in the context

of other Heplisav studies in the Summary of Clinical Safety (Attachment 3, pp. 82-93). The Applicant notes the following items in discussing the imbalance in the CSR: deaths due to cardiac disorders were balanced between treatment groups, there were some differences in specific cardiac-related medical history events between the treatment groups, and none of the events in the SMQ of myocardial infarction were assessed by investigators as related. Specific circumstances surrounding each event are also described. In the Summary of Clinical Safety, the integrated analysis, the Applicant additionally discusses the following: the temporal relationship between vaccination and the events, differences in baseline characteristics of subjects reporting MIs between treatment groups, the high prevalence of risk factors for cardiovascular disease at baseline, comparison of observed events to the National Heart, Lung, and Blood Institute (NHLBI) population estimates adjusted for age, sex, and race, and mechanisms of biologic plausibility. A presentation of the timing of events, the risk factors of those who reported MIs, and the baseline risk factors of all subjects by treatment group and by study appears below.

Timing and risk factors

Table 4 is a reviewer-generated summary of the 22 subjects reporting MI in DV2-HBV-23, the timing of the SAEs and the subject's risk factors for coronary disease. All subjects reporting events identified as MI had risk factors for cardiovascular disease and/or prior known cardiovascular disease. Within one week of the last active vaccination, one subject in the Heplisav group and none in the Engerix-B group reported an MI. Within one month, three subjects in the Heplisav group and one in the Engerix-B group reported an MI. Within three months, nine subjects in the Heplisav group and one in the Engerix-B group reported an MI. The remainder of MI events were reported more than three months after the last active injection.

Table 4. Timing of myocardial infarction following vaccination and baseline risk factors of subjects reporting myocardial infarction, by treatment group, Safety Population, DV2-HBV-23

Subject #	Study Day of MI event	Day of MI event relative to most recent active dose	Most recent active dose #	Age	Sex	Prior CAD	DM	HTN	DL	Smoked within prior year	Obesity
Heplisav											
141110	28	3	2	61	F	**?**		**+**			
130084†	8	8	1	50	M	**+**		**+**			
106312	14	14	1	64	F		**+**	**+**	**+**		
113011	81	53	2	68	F	**?**			**+**	**+**	
131091†	85	58	2	69	M			**+**	**+**	**+**	
134373	87	62	2	64	M			**+**	**+**		
112090	93	64	2	53	M		**+**	**+**	**+**		**+**
140099	87	64	2	65	M	**+**		**+**		**+**	
126206	113	85	2	68	M	**+**		**+**	**+**		**+**
122174*	123	96	2	56	M			**+**	**+**		**+**

Subject #	Study Day of MI event	Day of MI event relative to most recent active dose	Most recent active dose #	Age	Sex	Prior CAD	DM	HTN	DL	Smoked within prior year	Obesity
139037	202	174	2	39	F			+		+	
103189	203	175	2	46	M			+	+		+
101154	231	208	2	69	F				+		+
122613†	320	288	2	47	M		+				
122992	295	295	1	52	M			+			
115076	338	309	2	68	M		+	+	+		+
101118	347	319	2	62	M	+		+	+		+
130045	347	319	2	63	F		+	+			+
121050	356	329	2	60	M			+	+		
Engerix-B											
135070†	13	13	1	52	M					+	
112291	272	115	3	65	M	?	+	+	+		+
138102	371	203	3	54	M	+			+		

Source: Reviewer-generated analysis from 125428/0.42, Module 5.3.5.1, datasets ADSL, ADAE, and ADMH; 125428/0.74
Day 1 is day of administration. An event start day relative to the most recent dose of x is x-1 days following the most recent dose.
Risk factors were determined by datasets or noted in narrative.
MI: myocardial infarction, CAD: coronary artery disease, DM: diabetes mellitus, HTN: hypertension, DL: dyslipidemia
+ Subject has risk factor
? Narrative and datasets conflict
* Subject 122-174 had a cardiac catheterization showing no coronary artery disease
† Fatal event

Baseline characteristics of subjects in DV2-HBV-23

Baseline medical conditions reported by subjects in DV2-HBV-23 were similar between treatment groups. Most subjects reported at least one medical condition: 91.8% of subjects in the Heplisav and 91.1% of subjects in the Engerix-B group. The most commonly reported medical history terms by PT were hypertension (35.4% Heplisav, 34.6% Engerix-B), seasonal allergy (22.5% Heplisav, 23.1% Engerix-B), depression (17.0% Heplisav, 17.0% Engerix-B), osteoarthritis (16.5% Heplisav, 16.1% Engerix-B), gastroesophageal reflux disease (15.6% Heplisav, 15.6% Engerix-B), and hyperlipidemia (15.2% Heplisav, 14.7% Engerix-B).

Tables 5 and 6 summarize the risk factors for cardiovascular disease and pre-existing coronary artery ischemic disease between the two study groups. A CBER-generated assessment of hypertension was added to Table 5 as this was not included in the Applicant's Medical History and Baseline Characteristics table (Summary of Clinical Safety, Attachment 3, pp.84-86)

Table 5. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population, DV2-HBV-23

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
Type 2 Diabetes*	762 (13.6)	381 (13.7)
Hypertension†	2021 (36.2)	978 (35.2)

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
Hyperlipidemia‡	1757 (31.4)	879 (31.6)
Sex and Age: Male > 45 years	1879 (33.6)	919 (33.0)
Sex and Age: Female > 55 years	1028 (18.4)	537 (19.3)
Smoking within 1 year	1843 (33.0)	909 (32.7)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86
* Defined as subjects flagged by the Applicant as diabetic – subjects with a clinical diagnosis of diabetes and taking a hypoglycemic agent
† Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
‡ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow

Table 6. Number and proportion of subjects with medical conditions at baseline indicating cardiac ischemia, Safety Population, DV2-HBV-23

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
At least one baseline medical diagnosis of cardiac ischemia*	**211 (3.8)**	**99 (3.6)**
Coronary artery disease	140 (2.5)	65 (2.3)
Myocardial infarction	72 (1.3)	35 (1.3)
Coronary arterial stent insertion	56 (1.0)	27 (1.0)
Coronary artery bypass	47 (0.8)	16 (0.6)
Arteriosclerosis Coronary Artery	19 (0.3)	4 (0.1)
Angina Pectoris	18 (0.3)	12 (0.4)
Ischemic Cardiomyopathy	3 (0.05)	1 (0.04)
Myocardial ischemia	3 (0.05)	0
Coronary Artery Occlusion	2 (0.04)	2 (0.07)
Coronary artery stenosis	2 (0.04)	0
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	1 (0.02)	1 (0.04)
Angina unstable	1 (0.02)	1 (0.04)
Arteriospasm coronary	1 (0.02)	0
Prinzmetal angina	1 (0.02)	0
Silent myocardial infarction	1 (0.02)	0
Troponin increased	1 (0.02)	0
Coronary Angioplasty	0	5 (0.2)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86
* Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease

The Applicant presents an analysis of subjects in the diabetes group (DV2-HBV-23 CSR, Attachment 2, p. 61). As per their analysis, HbA1C at baseline, the proportion of subjects with one or more complications of diabetes (84.1% Heplisav, 82.2% Engerix-B), and the proportion of subjects who had diabetes for five or more years (66.7% Heplisav, 67.0% Engerix-B) were similar between the treatment groups. Of the diabetic subjects tested at Week 24, 19.2% of Heplisav subjects and 23.3% of Engerix-B subjects had HbA1C levels < 6.5%, 62.0% of

Heplisav subjects and 55.7% of Engerix-B subjects had HbA1C levels 6.5% to 9.0%, and 18.9% of Heplisav subjects and 21.1% of Engerix-B subjects had HbA1C levels > 9.0%. Consequently, at baseline, diabetic control was the same in both treatment groups. In contrast to baseline measurements, at Week 24, there are slightly more subjects in the Heplisav group with poorly controlled diabetes HgbA1C ≥ 6.5% (80.9%) compared to the Engerix-B group (76.7%).

Baseline characteristics in other Heplisav studies

As a primary objective of DV2-HBV-23 was to assess non-inferiority of Heplisav compared to Engerix-B in subjects with Type 2 diabetes, subjects enrolled in this study had different baseline characteristics than those enrolled in previous trials. Table 7 shows the demographics and Table 8 shows the baseline characteristics suggestive of increased cardiovascular risk of subjects in DV2-HBV-23, DV2-HBV-16, and other studies that used the final formulation of Heplisav. Tables 7 and 8 differ from that presented by the Applicant (Summary of Clinical Safety, Attachment 3, pp. 84-86) in that only studies utilizing the proposed formulation of Heplisav are included here, Study DV2-HBV-16 is presented separately given that major adverse cardiovascular events were identified in the study, and a CBER-generated assessment of hypertension was added. Subjects enrolled in DV2-HBV-23, reported more diabetes, hypertension, smoking, and history of cardiac ischemic disease than reported by subjects enrolled in other trials.

Table 7. Demographic characteristics, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, and -22)

Demographic characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16 Heplisav N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-10, -14, and -22* Heplisav N = 2042 n (%)	DV2-HBV-10, -14, and -22* Engerix-B N = 605 n (%)
Age: Mean (SD)	50.36 (11.74)	50.37 (11.68)	54.03 (7.89)	53.83 (7.81)	40.40 (9.45)	39.86 (9.01)
Age: Median	52	52	53	54	42	41
Age: Range	18 – 71	18 – 70	40 – 70	40 – 70	18 – 69	18 – 55
Sex: Male	2844 (50.9)	1391 (50.0)	943 (47.9)	236 (49.1)	938 (45.9)	261 (43.1)
Sex: Female	2743 (49.1)	1390 (50.0)	1025 (52.1)	245 (50.9)	1104 (54.1)	344 (56.9)
Race: White	3968 (71.0)	2007 (72.2)	1619 (82.3)	399 (83.0)	1868 (91.5)	555 (91.7)
Race: Black	1461 (26.1)	696 (25.0)	297 (15.1)	69 (14.3)	55 (2.7)	20 (3.3)
Ethnicity: Not Hispanic	5062 (90.6)	2541 (91.4)	1849 (94.0)	448 (93.1)	1990 (97.5)	581 (96.0)
Ethnicity: Hispanic	521 (9.3)	239 (8.6)	117 (5.9)	33 (6.9)	52 (2.5)	24 (4.0)

Source: Adapted from 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 10-5, p.60, Clinical Study Report DV2-HBV-16, Table 14.1.2-3, and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 dataset ADSL of integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group
n number of subjects reporting medical history item or characteristic
SD standard deviation
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 dataset ADSL of integrated studies

Table 8. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, and -22)

Condition or characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16* Heplisav N=1968 n (%)	DV2-HBV-16* Engerix-B N=481 n (%)	DV2-HBV-10, -14, and -22* Heplisav N = 2042 n (%)	DV2-HBV-10, -14, and -22* Engerix-B N = 605 n (%)
At least one baseline medical diagnosis of cardiac ischemia†	211 (3.8)	99 (3.6)	50 (2.5)	15 (3.1)	13 (0.6%)	2 (0.3%)
Type 2 Diabetes‡	762 (13.6)	381 (13.7)	158 (8.0)	33 (6.9)	48 (2.4)	11 (1.8)
Hypertension§	2021 (36.2)	978 (35.2)	579 (29.4)	143 (29.7)	239 (11.7)	57 (9.4)
Hyperlipidemia¶	1757 (31.4)	879 (31.6)	587 (29.8)	152 (31.6)	181 (8.9)	47 (7.8)
Sex and Age: Male ≥ 46 years	1879 (33.6)	919 (33.0)	776 (39.4)	195 (40.5)	330 (16.2)	76 (12.6)
Sex and Age: Female ≥ 56 years	1028 (18.4)	537 (19.3)	451 (22.9)	92 (19.1)	8 (0.4)	0
Smoking within 1 year	1843 (33.0)	909 (32.7)	431 (21.9)	118 (24.5)	703 (34.4)	224 (37.0)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)	863 (43.9)	205 (42.6)	542 (26.5)	167 (27.6)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86 and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of the integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group
n number of subjects reporting medical history item or characteristic
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of integrated studies
† Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease
‡ Defined as, in DV2-HBV-23, subjects identified as diabetic in the Diabetes History case report form; in DV2-HBV-16 and -10, subjects with a medical history term of diabetes and taking a drug with a WHO Drug ATC2 code of "DRUGS USED IN DIABETES"; in DV2-HBV-14 and -22, subjects with a medical history term of diabetes
§ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
¶ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow

CBER requested any additional analyses the Applicant had performed regarding the imbalance in myocardial infarction in a September 9, 2016 IR. In response, the Applicant submitted "Evaluation of acute myocardial infarction and major adverse cardiovascular events in the Phase 3 Heplisav clinical trials" (Attachment 4). In this document the Applicant presents the following analyses and conclusions based upon the three Phase 3 trials (DV2-HBV-10, -16, and -23):

- A presentation of treatment-emergent events coded to the preferred terms of the MedDRA MI SMQ narrow, as discussed above, demonstrated that the imbalance was due to an observation in one preferred term (AMI) in one study (DV2-HBV-23).
- A multivariate logistic regression analysis with MI events as the dependent variable, and age, sex, race, hypertension, BMI, diabetes mellitus, smoking, history of MI or stroke, and treatment group as the independent variables, demonstrated that only hypertension (Odds Ratio [OR] = 3.78; 95% CI: 1.44, 9.91) and age (OR = 1.07 per one year increase; 95% CI: 1.02, 1.13) were statistically significant independent predictors of MI. Treatment group was not a significant independent predictor of events identified by the MI SMQ (OR = 2.21; 95% CI: 0.76, 6.45).
- A Major Adverse Cardiovascular Events (MACE) analysis, described below.
- An analysis of causality based upon seven Bradford Hill criteria, in which they conclude that none of the criteria support causality (temporality, strength/effect size, consistency, coherence, specificity, biologic plausibility, and analogy) (pp. 22 – 33).

MACE Analysis

As described on page 10 of the document, preferred terms selected to identify potential MACE outcomes were chosen in a blinded manner by Darren McGuire, M.D. (Professor of Medicine at the University of Texas Southwestern). Dr. Steven Nissen's Cleveland Clinic Coordinating Center for Clinical Research (C5Research) performed independent and blinded post-hoc adjudication of all potential MACE events, categorizing events as 1) a MACE event, 2) not a MACE event, or 3) insufficient information to make a determination. Observed and expected rates and numbers of adjudicated MACE events were compared. Expected rates and numbers were estimated by applying person-years of follow up by age group, sex, and race for 35- to 70-year old whites and blacks in HBV-16 and HBV-23 to population-based data in the United States for each MACE component: 1) cardiovascular death (US Vital Statistics data from the US Centers for Disease Control and Prevention); 2) myocardial infarction (Mozaffarian, Benjamin, et al. 2015); and 3) stroke (Mozaffarian, Benjamin, et al. 2015). Expected numbers of events were also estimated using risk prediction models based on baseline cardiovascular risk factors.

The results of the subjects identified as reporting an adjudicated MACE event in the three pivotal trials are presented in Table 9 (see also Attachment 4, p. 16). The Applicant reports that no MACE events were identified in DV2-HBV-10. A list of the subjects considered for reporting a MACE and adjudicated as reporting a MACE can be found in Attachment 5, Listing 7.1 (pp. 55 – 72) and Listing 7.2 (pp. 73 – 86), respectively. Table 9 contrasts with the table presented by the Applicant in that it also includes additional columns for the MACE events identified in

studies DV2-HBV-16 and -23, excluding -10. Studies DV2-HBV-16 and -23 were the pivotal trials that monitored SAEs for approximately one year following vaccination. DV2-HBV-10 followed subjects for 28 weeks following the first vaccination. The table presented here also includes 95% and 90% CIs calculated using the exact method, which CBER statisticians recommend for evaluating these safety events. The Applicant then compares the rates and numbers of adjudicated major cardiovascular events observed in the three Phase 3 trials to expected rates obtained by age, sex, and race adjusted estimates from population-based data and to expected rates obtained by risk prediction models that account for cardiovascular risk factors in the study populations. The Applicant concludes that the observed number of major cardiovascular events in Heplisav recipients is similar to or lower than expected and that the observed number of major cardiovascular events in Engerix-B recipients is lower than expected, and thus, the imbalance in events coded to the preferred term AMI appears to be due to a lower than expected number of events in the Engerix-B group as opposed to an excess of events in the Heplisav group.

The information provided in this consult request is a summary. Any additional information that has not been included and would be helpful, such as datasets or analyses, can be provided upon request. The Applicant submitted the response to the November 10, 2016 CR on February 7, 2017. There may be additional information to consider, pending review of the submission, which would require an update to the consult.

Table 9. Applicant-identified, treatment-emergent, serious three-point adjudicated major adverse cardiovascular events by treatment group, DV2-HBV-16, DV2-HBV-23, -16 and -23 combined, and the pivotal studies combined (DV2-HBV-10, -16, and -23) (Total Safety Populations)

	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-23 Relative Risk (95% CI)[a] (95% CI)[e] (90% CI)[e]	DV2-HBV-16 Heplisav N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-16 Relative Risk (95% CI)[a] (95% CI)[e] (90% CI)[e]	DV2-HBV-16 and -23 Heplisav N = 7555 n (%)	DV2-HBV-16 and -23 Engerix-B N = 3262 n (%)	DV2-HBV-16 and -23 Relative Risk (95% CI)[a] (95% CI)[e] (90% CI)[e]	DV2-HBV-10, -16 and -23 Heplisav N = 9365 n (%)	DV2-HBV-10, -16 and -23 Engerix-B N = 3867 n (%)	DV2-HBV-10, -16 and -23 Relative Risk (95% CI)a (95% CI)e (90% CI)e
Composite 3-point MACE events	28 (0.50)	6 (0.22)	2.32 (0.96, 5.60) (0.98, 7.52) (1.00, 6.32)	3 (0.15)	2 (0.42)	0.37 (0.06, 2.19) (0.06, 3.69) (0.08, 1.99)	31 (0.41)	8 (0.25)	1.67 (0.77, 3.64) (0.78, 6.36) (0.88, 3.55)	31 (0.33)	8 (0.21)	1.6 (0.74, 3.48) (0.75, 6.08) (0.84, 3.40)
Cardiovascular death*	3 (0.05)	1 (0.04)	1.49 (0.16, 14.35) (0.15, 38.32) (0.22, 18.98)	1 (0.05)	1 (0.21)	0.24 (0.02, 3.9) (0.01, 8.20) (0.01, 4.09)	4 (0.05)	2 (0.06)	0.86 (0.16, 4.71) (0.15, 6.54) (0.18, 4.28)	4 (0.04)	2 (0.05)	0.83 (0.15, 4.51) (0.15, 6.26) (0.18, 4.10)
Myocardial infarction†	14 (0.25)	1 (0.04)	6.97 (0.92, 52.97) (1.00, 184.9) (1.46, 91.31)	2 (0.10)	1 (0.21)	0.49 (0.04, 5.38) (0.04,13.31) (0.06, 6.61)	16 (0.21)	2 (0.06)	3.45 (0.79, 15.01) (0.88, 35.33) (1.00, 21.52)	16 (0.17)	2 (0.05)	3.30 (0.76, 14.36) (0.84, 33.80) (1.00, 20.58)
Stroke‡	11 (0.20)	4 (0.14)	1.37 (0.44, 4.30) (0.44, 7.46) (0.54, 4.05)	0	0	-	11 (0.15)	4 (0.12)	1.19 (0.38, 3.73) (0.38, 6.48) (0.46, 3.51)	11 (0.12)	4 (0.10)	1.14 (0.36, 3.56) (0.37, 6.19) (0.45, 3.36)

Source: Adapted from 125428/0.65, Module 2.7.4, Evaluation of acute myocardial infarction and major adverse cardiovascular events in the Phase 3 Heplisav clinical trials, Table 3-3, p. 16

Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.

N number of subjects in each treatment group

n number of subjects reporting adverse event

CI confidence interval

MACE major adverse cardiovascular events

a Asymptotic confidence interval

e Exact confidence interval

* Cardiovascular cause of death comprises the following preferred terms: Death from cardiovascular cause includes death due to Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.

† Myocardial infarction includes deaths due to myocardial infarction and comprises the following preferred terms: Myocardial infarction includes Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, or Silent Myocardial Infarction.

‡ Stroke includes deaths due to stroke and comprises the following preferred terms: Stroke includes Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Haemorrhagic Stroke, Haemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain

Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischaemic Cerebral infarction, Ischaemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke.

Questions for the consultant

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2-HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

    a. In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

    b. Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

    c. In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered

to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.
6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

Appendix A – List of Attachments

1. **Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events provided by the Applicant**
2. **DV2-HBV-23 Clinical Study Report**
3. **Summary of Clinical Safety**
4. **Response to IR, Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials**
5. **Integrated Summary of Safety - SCS Tables and Listings**

Appendix B – Death Narratives

Below are brief narratives of deaths in the cardiac disorders and general SOC. Subjects who received Heplisav are presented first. Detailed narratives submitted by the Applicant are available in Attachment 1.

Heplisav

Subject 130-084 was a 50-year-old black man with a relevant medical history of colon cancer, hypertension, dyspnea, mitral valve prolapse and prior mitral valve replacement surgery, COPD, coronary atherosclerosis, cardiomyopathy, left ventricular hypertrophy, and alcohol and cocaine abuse. He was found dead at home (b) (6) days after his first injection of Heplisav with no sign of trauma. The cause of death per the death certificate was "acute coronary syndrome, secondary to atherosclerosis" with cardiomyopathy, left ventricular hypertrophy and alcohol abuse as contributory factors. No autopsy was performed (PT = acute coronary syndrome).

Subject 131-091 was a 69-year-old white man with a relevant medical history of hypertension, edema, chronic renal failure, congestive heart failure, COPD, acute respiratory failure, supplemental oxygen, abdominal aortic aneurysm, neuropathy, and smoking. He was found dead in his home (b) (6) days after his second injection of Heplisav. The cause of death listed in the death certificate was acute myocardial infarction due to atherosclerosis. An autopsy was not performed (PT = acute myocardial infarction).

Subject 112-311 was a 57-year-old white man with hypertension, type 2 diabetes mellitus, diabetic peripheral neuropathy, microalbuminuria, acute kidney injury, and diabetic gastroparesis who was found dead in his home. An autopsy determined that the subject died as a result of hypertensive cardiovascular disease (b) (6) days after his second Heplisav injection. Yellow atherosclerotic plaques were seen in the left anterior descending artery. Toxicology testing was positive for alcohol and cyclobenzaprine, but it was determined this did not contribute to his death.

Subject 132-082 was a 63-year-old white man with hypertension and depression who was found dead on the living room floor (b) (6) days after dose 2 of Heplisav. An external exam determined the death was due to hypertensive heart disease.

Subject 138-012 was a 58 year-old black woman with medical history of obesity and hypertension who died in her sleep (b) (6) days following dose 2 of Heplisav. Autopsy was performed and demonstrated hypertensive cardiovascular disease, focal coronary atherosclerosis, severe pulmonary congestion, cerebrovascular disease with a small lacunar infarct in left basal ganglia, hepatomegaly and macrovesicular steatosis, and glomerulosclerosis. The cause of death was reported as hypertensive cardiovascular disease with (morbid) obesity noted as a contributing factor.

Subject 133-120 was a 71-year-old white woman with obesity, hypertension, type 2 diabetes mellitus, stroke, and high cholesterol, who died from a cardiac arrest (b) (6) days after her dose 2 of Heplisav. A death certificate reported that the subject died of a cardiac arrest which was due or was a consequence of the subject's medical history of diabetes. An autopsy was not performed.

Subject 122-613 was a 47-year-old black man with a relevant medical history of type 2 diabetes, peripheral vascular disease, gangrene left leg, left leg below the knee amputation and right leg edema. (b) (6) days after his second dose of Heplisav, the subject experienced a fatal myocardial infarction and died in the hospital. A death certificate, autopsy results, and hospital records were not available (PT = myocardial infarction).

Subject 104-152 was a 56-year-old white woman with depression and possible alcohol abuse who was found unresponsive at home (b) (6) days after dose 2 of Heplisav. She was noted to be pale with bruising on her upper extremities, and to have jugular venous distension and tracheal deviation. She was transported to an emergency department where she underwent resuscitative efforts that were ultimately unsuccessful. Her final diagnoses included cardiopulmonary arrest, gastrointestinal bleed, and thrombocytopenia. A death certificate was unavailable and an autopsy was not performed.

Subject 119-318 was a 61 year-old white woman with medical history of enlarged heart, depression, and anxiety who died (b) (6) days following dose 2 of Heplisav. The Applicant has no information regarding the cause of death. The subject had been considered lost to follow-up. Her death was discovered through the reengagement program.

Subject 119-290 was a 52-year-old white woman with a medical history of headaches, depression, anxiety, and insomnia per study records. Additional history of hypertension, bipolar disorder, and heavy smoking was provided in the subject's medical and coroner's records. The subject was found dead (b) (6) days after dose 2 of Heplisav, sitting on her couch at home with no signs of foul play, alcohol, or drug abuse. The Applicant reports that the initial report of this event was Death – accidental overdose. The preferred term was changed to Death when it was determined that no autopsy results would be available.

<u>Engerix-B</u>

Subject 135-070 was a 52-year-old white man with a relevant medical history of tobacco and marijuana use who was found down in a parking lot (b) (6) days after his first injection of Engerix-B. He died after unsuccessful resuscitative efforts with ventricular fibrillation arrest due to acute myocardial infarction listed as the cause of death. An autopsy determined that the cause of death was atherosclerotic cardiovascular disease (PT = myocardial infarction).

Subject 119-175 was a 48 year-old black man with a medical history of hypertension, gout, and alcohol abuse who was found dead in the bed of a motel room. An empty beer can and an empty pint of vodka were found on the floor, as well as signs of tobacco and possible marijuana use. No autopsy was performed but a chest x-ray was consistent with pulmonary edema. Toxicology results included blood ethanol 0.32 gm/dL, vitreous ethanol 0.45 gm/dL, and other drugs of abuse. The coroner determined the cause of death to be hypertensive heart disease with contributory factors of cocaine, heroin, and ethanol use.

Subject 130-392 was a 70 year-old black man with relevant medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, patent foramen ovale, congestive heart failure, transient ischemic attack, anemia, and COPD (diagnosed on-study) who reported a cough, progressing to weakness, nausea, and vomiting, for which he was admitted. He had a bandemia of 25. Shortly after admission, he was found unresponsive. During the hospitalization, he was diagnosed with aspiration pneumonia, cerebrovascular accident, sepsis, acute renal failure, and gastrointestinal bleed. He was eventually transferred to a nursing home, where he was found unresponsive in cardiopulmonary arrest that occurred as he was eating dinner and died. No autopsy was performed.

Appendix C – Non-fatal Myocardial Infarction Narratives

Below are brief narratives of non-fatal SAEs identified by the SMQ Narrow for myocardial infarction. Subjects who received Heplisav are presented first. Detailed narratives submitted by the Applicant are available in Attachment 1.

Heplisav

Subject 141-110 was a 61-year-old Hispanic woman with a relevant medical history of chest pain, and hypertension who experienced a non-ST elevation myocardial infarction two days after the second injection of Heplisav, which was confirmed by cardiac catheterization with stent and balloon angioplasty performed (PT = acute myocardial infarction).

Subject 106-312 was a 65-year-old white woman with a relevant medical history of type 2 diabetes, dyslipidemia, hypertension, coronary artery disease, heart palpitations, and sleep apnea. Twenty-four days following dose 1 of Heplisav she was seen by a cardiologist for three days of worsening heart palpitations and was prescribed isosorbide mononitrate. A percutaneous coronary intervention was attempted on an unknown date in the same month as dose 2, but was unsuccessful. The subject discontinued the isosorbide mononitrate due to side effects. Three weeks following dose 2 she informed the site she was scheduled for cardiac catheterization. Five weeks after dose 2, a cardiac nuclear perfusion scan performed showed ischemic changes. She underwent a cardiac catheterization, which demonstrated multi-vessel coronary artery disease and total occlusion of her third obtuse marginal artery. Four cardiac stents were placed. The Applicant conservatively considers the onset of this event to be 14 days after the first injection of Heplisav as the date of the first catheterization is unknown (PT = coronary artery occlusion).

Subject 113-011 was a 68-year-old white woman with a relevant medical history of COPD, hyperlipidemia, coronary artery disease (noted in datasets, not in narrative), and tobacco use who reported an inferior myocardial infarction, confirmed by cardiac catheterization with stent placement 51 days following the second dose of Heplisav (PT = myocardial infarction). Following the procedure she had an SAE of episodes of non-sustained ventricular tachycardia.

Subject 134-373 was a 64-year-old white man with a relevant medical history of hyperlipidemia, hypertension, and tobacco use who reported an ST elevation myocardial infarction 61 days after his second injection of Heplisav, confirmed with cardiac catheterization with three stents placed(PT = acute myocardial infarction).

Subject 112-090 was a 53-year-old white man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes, morbid obesity, sleep apnea, multiple prior abdominal surgeries, and alcoholism. He was admitted to the hospital with abdominal

pain, diarrhea, a partial small bowl obstruction, and acute kidney injury due to dehydration and diarrhea. He was treated medically and improved. On hospital day 3, he experienced a non-ST elevation myocardial infarction 63 days after his second injection of Heplisav. A cardiac catheterization showed multi-vessel disease and three stents were placed (PT = acute myocardial infarction).

Subject 140-099 was a 66-year-old white man with a relevant medical history of hypertension, coronary artery disease post-percutaneous intervention one year prior to study enrollment, and tobacco use. The subject experienced an ST elevation myocardial infarction 64 days after his second injection of Heplisav, confirmed by cardiac catheterization with stent placement (PT = acute myocardial infarction). A possible LV thrombus was noted and the subject was given anticoagulants. The subject went on to report SAEs of acute systolic heart failure, pulmonary embolism, and LV thrombus 284 days after dose 2.

Subject 126-206 was a 68-year-old white man with a relevant medical history of coronary artery disease, prior MI with cardiac stent placement, hypertension, high cholesterol, sleep apnea on continuous positive airway pressure, deep vein thrombosis, Factor V Leiden mutation (unknown at study enrollment), and paroxysmal atrial fibrillation. He experienced an acute myocardial infarction with cardiogenic shock, requiring percutaneous intervention, intra-aortic balloon pump, and left ventricular assist device placement, 84 days after his second injection of Heplisav (PT = acute myocardial infarction).

Subject 122-174 was a 56-year-old white man with a relevant medical history of hypertension, gout, hypercholesterolemia, septic shock, deep venous thrombosis, paroxysmal atrial fibrillation, morbid obesity, and prior tobacco use. During the study, he had multiple hospitalizations for urosepsis, atrial fibrillation, and latent tuberculosis (rule out active tuberculosis). The narrative states the subject lived in a shelter. He was admitted for unstable angina 95 days after his second injection of Heplisav, reporting intermittent chest pain for the previous three weeks. A perfusion scan showed a reversible/partially reversible defect, but a cardiac catheterization showed “no significant coronary artery disease.” He had multiple subsequent hospitalizations, including for dyspnea and mycobacterium avium intracellular complex infection (PT = unstable angina). Based on the negative cardiac catheterization, this event is not included in CBER’s final count of MIs.

Subject 139-037 was a 39-year-old white woman with a relevant medical history of tobacco use, asthma, and hypertension. The subject experienced a non-ST elevation myocardial infarction 173 days after her second injection of Heplisav, confirmed with cardiac catheterization and stent placement (PT = acute myocardial infarction).

Subject 103-189 was a 47-year-old white man with a relevant medical history of hyperlipidemia, sleep apnea, hypertension, obesity, and low testosterone (taking testosterone). He experienced a non-ST elevation myocardial infarction 175 days after the second injection of Heplisav. Troponin-1 was elevated to 11.48 ng/mL. Cardiac catheterization showed ectasia of left circumflex and left anterior descending with signs of a recent ruptured plaque in the proximal left anterior descending. Medical management was recommended (PT = acute myocardial infarction).

Subject 101-154 was a 70-year-old white woman with a relevant medical history of obesity and dyslipidemia who reported a non-ST elevation myocardial infarction 207 days after the dose 2 of Heplisav. Troponin I was elevated to 10.3 ng/mL. She received a catheterization, which showed diffuse non-obstructive coronary artery disease with wall motion abnormalities suggesting the first diagonal branch as the culprit vessel. There was no evidence of an active lesion, no percutaneous intervention, and the subject was treated medically (PT = acute myocardial infarction).

Subject 122-992 was a 53-year-old black man with a relevant medical history of prior heroin addiction, hypertension, and prostate cancer, diagnosed prior to vaccination. He was discontinued from treatment at Week 4 when the site became aware of his prostate cancer. He reported an ST-elevation myocardial infarction 294 days after the first injection of Heplisav, confirmed by coronary angiogram and treated with stent placement (PT = acute myocardial infarction).

Subject 115-076 was a 69-year-old white man with a relevant medical history of obesity, type 2 diabetes, hypertension, hyperlipidemia and prior tobacco use. He was taking phentermine beginning three years prior to study enrollment. The narrative reports the subject was seen by his primary care physician twice after study start for chest pressure, diagnosed as indigestion. These events are not reported as MAEs. He reported chest pain, was found have paroxysmal ventricular tachycardia, followed by and atrial fibrillation with rapid ventricular response 308 days after the second injection of Heplisav. Blood pressure of 192/107 mmHg is also reported. He was placed on anti-arrhythmics and multiple attempts at cardioversion were unsuccessful. He was then diagnosed with a non-ST elevation myocardial infarction (PT = acute myocardial infarction). Cardiac catheterization showed severe single-vessel coronary artery disease with thrombus, requiring thrombectomy and percutaneous intervention. Subsequently, he had a cardiac arrest and an implantable cardiac defibrillator was implanted.

Subject 101-118 was a 63-year-old white man with a relevant medical history of dyslipidemia, obesity, coronary artery disease with two prior percutaneous interventions with stent placement, and hypertension. The narrative also notes a prior myocardial infarction. He experienced an ST elevation myocardial infarction while mowing his lawn

318 days after the second injection of Heplisav. He received cardiac catheterization with stent placement (PT = acute myocardial infarction).

Subject 130-045 was a 64-year-old white woman with a relevant medical history of type 2 diabetes, hypertension, obesity, peripheral vascular disease, sleep apnea, and chronic kidney disease. She experienced a non ST-elevation myocardial infarction 318 days after her second injection of Heplisav, confirmed by cardiac catheterization with stent placement (PT = acute myocardial infarction).

Subject 121-050 was a 61-year-old white man with a relevant medical history of hypertension, low testosterone (on testosterone), and hypercholesterolemia who experienced an ST-elevation myocardial infarction 328 days after the second injection of Heplisav, confirmed by cardiac catheterization with three stents placed (PT = acute myocardial infarction).

Engerix-B

Subject 112-291 was a 66-year-old white man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes, obesity, chronic kidney disease stage III, and possible coronary artery disease (noted in narrative, not in datasets). He had a syncopal episode and was diagnosed with a non-ST elevation myocardial infarction 113 days after his third injection of Engerix-B. He underwent a six-vessel coronary artery bypass graft (PT = acute myocardial infarction).

Subject 138-102 was a 55-year-old black man with a relevant medical history of angina due to possible arterial blockage, dyslipidemia, and former alcohol and cocaine dependency. As part of the evaluation for knee surgery the subject had a cardiac catheterization that showed multi-vessel disease. Nine days later and 202 days following the third dose of Engerix-B, the subject reported chest pain and underwent coronary artery bypass grafting (CABG) (PT = coronary artery occlusion).

Appendix D – Narratives provided by the Applicant for Subjects Identified with Major Adverse Cardiovascular Events in DV2-HBV-16

Study: DV2-HBV-16

Site/Subject Number: 92-638

Treatment Group: Engerix-B

SAE Verbatim Term: Heart failure

SAE Preferred Term: Cardiac failure

Event Outcome: Fatal

Subject 92-638 was a 64-year-old black or African American man with a medical history that included gout since 1998, hypertension since 2000, reflux since 2006, and osteoarthritis in both knees since 2009.

Concomitant medications included perindopril, amlodipine, allopurinol, indomethacin, rabeprazole, diclofenac, bisoprolol, ventolin, and deglycyrrhizinated licorice root extract.

The subject received study injections on 12 May 2010 and 10 June 2010. On (b) (6) days after his second and last study injection, the subject was hospitalized in critical condition following a heart attack. On 24 July 2010, the subject experienced pulmonary arrest and ventricular fibrillation. The subject received emergency cardiac medications and cardioversion, but his heart continued to fail. On (b) (6), the subject expired; no autopsy was performed.

The subject's laboratory results at screening on 10 May 2010 were normal except for creatinine 110.5 mg/dL (< 103.0 mg/dL), neutrophils 77.0% (43.0 - 73.0%), and platelets 108 × 109/L (145 - 390 × 109/L).

The investigator assessed the event of heart failure as an important medical event that required hospitalization, resulted in death, and was not related to study treatment.

Study: DV2-HBV-16

Site/Subject Number: 22-003

Treatment Group: Heplisav Lot TDG006

SAE Verbatim Term: Pulmonary embolism

SAE Preferred Term: Pulmonary embolism

Event Outcome: Fatal

Subject 22-003 was a 46-year-old white man with no relevant medical history including no prior history of coagulation disorder. There was no pre-disposing cause for pulmonary embolism; he was an active adult without preceding trauma to cause pulmonary embolism.

He was not taking any concomitant medications.

The subject received study injections on 12 March 2010 and 9 April 2010. On (b) (6) days after his second study injection, the subject experienced swelling and leg pain, right pressure in his chest, and shortness of breath; he had been playing softball and collapsed. He was resuscitated on the field by emergency medical technicians but died on his way to the hospital. An emergency medical technician report was not available; a copy of the autopsy report was requested repeatedly but not received. The only source document available supporting the diagnosis of pulmonary embolism was a report about a telephone conversation between study site personnel and the subject's friend.

The subject's laboratory results at Visit 3 on 8 May 2010 were within normal limits.

The investigator assessed the event of pulmonary embolism as fatal and not related to study treatment.

Study: DV2-HBV-16

Site/Subject Number: 41-335

Treatment Group: Heplisav Lot TDG008

SAE Verbatim Term: Non-ST segment elevation myocardial infarction

SAE Preferred Term: Acute myocardial infarction

Event Outcome: Resolved

Subject 41-335 was a 58-year-old white man with a medical history that included gastroesophageal reflux disease and nocturia. His surgical history included shoulder surgeries for rotator cuff tears and a vasectomy.

Concomitant medications included omeprazole.

The subject received study injections on 4 May 2010, 2 June 2010, and 13 October 2010. On (b) (6) days after the first study injection, the subject presented to the emergency room with a 2-week history of episodic non-radiating retrosternal chest pain associated with shortness of breath precipitated by activity and relieved with rest. The symptoms had started on 11 May 2010. The longest episode of pain, which lasted 15 to 20 minutes, was noted to be 'very significant for unstable angina.' The subject experienced discomfort along with shortness of breath and diaphoresis while walking 2 blocks from his car to the emergency room. He reported that he had a stress test done 2 years previously due to palpitations but had no known coronary disease. On 25 May 2010, an ECG and a chest x-ray were both normal. Serial troponin levels on 25 May 2010 were mildly elevated at 0.10, 0.09, and 0.12 ng/mL (0 - 0.05 ng/mL). Other laboratory values included hemoglobin 13.7 g/dL (14.0 - 18.0 g/dL), cholesterol 179 mg/dL (≤ 199 mg/dL), triglycerides 99 mg/dL (≤ 149 mg/dL), LDL cholesterol 115 mg/dL (≤ 100 mg/dL), and HDL cholesterol 44 mg/dL (40 - 60 mg/dL). Physical examination showed a regular rate and rhythm, normal S1 and S2 without murmurs, rubs, or gallops, and no lower extremity swelling or cyanosis. His vital signs were as follows: blood pressure 129/82 mmHg, heart rate 50 bpm, temperature 97.9°F, and oxygen saturation 98%. The subject was diagnosed with non-ST segment elevation myocardial infarction, admitted to the hospital, and managed with a heparin drip until angiography was performed. Angiography revealed severe stenosis of the left anterior descending (LAD) artery and right coronary artery (RCA). The subject underwent a percutaneous coronary intervention (PCI) to 3 areas; 2 in the LAD artery and 1 in the RCA. On 26 May 2010, the subject was discharged with simvastatin, lisinopril, metoprolol, clopidogrel, acetaminophen, aspirin, and nitroglycerin. Discharge diagnoses included coronary artery disease, unstable angina with borderline elevated troponins, and dyslipidemia. The event of non-ST-segment-elevation myocardial infarction was considered resolved on 26 May 2010. No action was taken with regard to study treatment.

The investigator assessed the event of non-ST segment elevation myocardial infarction as severe in intensity and not related to study treatment.

Study: DV2-HBV-16

Site/Subject Number: 20-610

Treatment Group: Heplisav Lot TDG006

SAE Verbatim Term: Myocardial infarction-non-ST segment elevation

SAE Preferred Term: Acute myocardial infarction

Event Outcome: Resolved with sequelae

Subject 20-610 was a 63-year-old white woman with a medical history that included hypertension since 2007, ischemic cardiomyopathy, heart attack in 1988, and hypercholesterolemia since 2003 that was not treated with statins due to elevated liver enzymes.

Concomitant medications included ramipril, aspirin, esomeprazole magnesium, vitamin D, levocetirizine dihydrochloride, and methenamine.

The subject received study injections on 1 March 2010, 30 March 2010, and 19 August 2010. On 12 April 2010, 14 days after the second study injection, the subject experienced severe substernal chest pain and went to the emergency room late at night. She was hospitalized on (b) (6) and diagnosed with a non-ST segment elevation myocardial infarction. Her troponin level was 1.48 ng/mL. Cardiac catheterization showed 80% stenosis of the mid right coronary artery and non-obstructive disease in the diagonal branch. The subject was transferred to another hospital for percutaneous coronary intervention of the proximal-to-mid right coronary artery with a 4 × 18 mm vision stent on (b) (6) . The subject tolerated the procedure well. During her hospitalization she was also found to have ischemic cardiomyopathy with an ejection fraction of 30-35%; treatment with metoprolol tartrate was initiated. The event was considered resolved with sequelae (ischemic cardiomyopathy with an ejection fraction of 30 - 35%) when the subject was discharged on 15 April 2010. Her discharge medications included clopidogrel bisulfate, aspirin, ramipril, simvastatin, and metoprolol. No action was taken with regard to study treatment.

The subject's laboratory results on 24 February 2010, 1 March 2010, and 30 March 2010 were normal with the exception of an elevation in creatinine on 24 February 2010 and 1 March 2010 (1.03 mg/dL on both dates; reference range < 0.97 mg/dL).

The investigator assessed the event of myocardial infarction-non-ST segment elevation as severe in intensity and not related to study treatment.

Study: DV2-HBV-16

Site/Subject Number: 29-614

Treatment Group: Engerix-B

SAE Verbatim Terms: Non ST segment elevation/myocardial infarction; Unstable angina

SAE Preferred Terms: Acute myocardial infarction; Angina unstable

Event Outcome: Resolved (both events)

Subject 29-614 was a 60-year-old white man with a medical history that included hypertension since 1990 (controlled since 2008), dyslipidemia, hearing loss, kidney stones, appendectomy, and a sprained wrist.

Concomitant medications included lisinopril.

The subject received study injections on 26 April 2010, 24 May 2010, and 13 October 2010. The subject reported that on 2 June 2010 he had what he described as indigestion starting at 15:00 hours after eating a 'big greasy hamburger.' The indigestion worsened and he developed chest pain at midnight on 3 June 2010, 10 days after the second study injection. He also had severe arm pain and severe headache. His wife called 911 and he was taken to the hospital then transferred to a larger hospital where it was reported that the subject had high blood pressure on arrival. The subject reported a several month history of exertional chest pain that was relieved with rest. The pain had been increasing in frequency and severity. His vital signs were as follows: blood pressure 145/88 mmHg, pulse 55 bpm, respiratory rate 12 breaths per minute, and oxygen saturation 100%. Physical examination results were within normal limits. His creatinine level was 1.6 mg/dL (0.5 - 1.4 mg/dL. Serial cardiac isoenzymes revealed a peak abnormal troponin of 0.98 ng/mL but total CK-MB was normal. His treatment included an ACE inhibitor and beta blocker therapy for blood pressure control. The subject had some relief of his chest pain after treatment of his blood pressure, but the chest pain continued intermittently overnight. Because his brain natriuretic peptide was 9 ng/L, the subject underwent a cardiac catheterization and was found to have severe multivessel coronary artery disease. He underwent a successful percutaneous transluminal coronary angioplasty (PTCA) with 2 stents deployed in the proximal to mid and the mid right coronary artery. His ejection fraction was normal. There were no post-procedure complications. The subject was monitored for 2 days. On 5 June 2010, laboratory values included an elevated cholesterol level of 214 mg/dL (120 - 200 mg/dL), and normal triglyceride and HDL cholesterol levels. His vital signs on the day of discharge included a blood pressure of 128/77 mmHg and a heart rate of 78 bpm. The subject was discharged home with clopidogrel, metoprolol, simvastatin, aspirin, hydrochlorothiazide, and nitroglycerin. The events were considered resolved on 5 June 2010. No action was taken with regard to study treatment.

The investigator assessed the events of non-ST segment elevation myocardial infarction and unstable angina as severe in intensity and not related to study treatment.

Shari L. Targum, M.D., M.P.H.
Division of Cardiovascular and Renal Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: April 6, 2017

FROM: Shari L. Targum, MD, MPH, Clinical Team Leader
Division of Cardiovascular and Renal Products, HFD-110

Shari L. Targum -S

THROUGH: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products, HFD-110

Norman L. Stockbridge -S

TO: Darcie Everett, MD, M.P.H., Medical Officer, OVRR/Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER

SUBJECT: Request for consultation regarding BLA #125428/0
NAME OF DRUG: Hepatitis B Vaccine (recombinant) adjuvant
TRADE NAME: HEPLISAV-B
RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A

SPONSOR: Dynavax Technologies Corporation

DOCUMENTS AVAILABLE FOR REVIEW: 1. Consultation request; 2. Summary document; 3. Applicant's Response to Information Request, including Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials; 4. Narratives of Deaths, other serious events;
DATE CONSULT RECEIVED: March 1, 2017
DESIRED COMPLETION DATE: April 3, 2017
DATE CONSULT COMPLETED: April 6, 2017

RATIONALE FOR CONSULT:
CBER is seeking advice on a comprehensive evaluation of the imbalance in AMI to support an evaluation of the risk-benefit profile of the hepatitis B vaccine (Heplisav).

BACKGROUND:
In 2012, Dynavax Technologies Corporation (Applicant) submitted Biologics License Application (BLA) 125428/0 for Heplisav– a new vaccine for prevention of hepatitis B infections in adults 18 - 70 years of age. On November 15, 2012, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) voted 8 to 5 that the safety data available for Heplisav were not adequate to support licensure, due to insufficient numbers in the safety database for a novel adjuvant. The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration subsequently issued a Complete Response (CR) letter, citing the need for further clinical safety evaluations to obtain a larger safety database.

In response, the Applicant conducted DV2-HBV-23, a randomized safety study in 8,300 subjects, comparing Heplisav (5500 subjects) to Engerix-B (2750 subjects). The results of this trial were submitted to the BLA March 16, 2016. A numerical imbalance in the unsolicited adverse event (MedDRA preferred term) acute myocardial infarction (AMI) was observed in this trial (14 subjects who received Heplisav, 1 subject who received Engerix-B). This imbalance had not been noted in previous smaller trials. CBER

sent an information request (IR) on September 9, 2016, which included a request for any additional analyses regarding the imbalance in AMI the Applicant had conducted. The Applicant responded via several submissions to the BLA from September 26, 2016 – October 11, 2016. CBER issued another CR letter on November 10, 2016, which included the items in the September 9th IR, as well as several additional items. The Applicant submitted the response to the CR on February 7, 2017, which is currently under review.

Product

Heplisav is a vaccine comprised of recombinant hepatitis B surface antigen (rHBsAg) combined with 1018 immunostimulatory sequence (ISS), a synthetic unmethylated cytosine phosphoguanine (CpG) enriched phosphorothioate oligodeoxynucleotide (ODN) adjuvant. Currently, there are no other licensed vaccines in the U.S. containing this adjuvant *(Reviewer comment: are there vaccines licensed outside the U.S. containing this adjuvant and, if so, are there safety data?)* The proposed indication is for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age. Each 0.5 mL dose contains 20 mcg of rHBsAg and 3000 mcg of the 1018 ISS adjuvant. The proposed dosing regimen is two 0.5 mL doses administered one month apart. Although safe and effective hepatitis B vaccines have been available for years, the Applicant notes the potential for improved immunologic response in certain subsets of individuals and the requirement for fewer doses (two vs. three doses) over a shorter period of time (one vs. six months), compared to available products, as the rationale for Heplisav's development.

Mechanism of Action:

Heplisav is proposed to act by using an adjuvant that activates toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells (pDCs) which, combined with HBsAg, leads to production of HBsAg-specific antibodies. The Applicant attributes activity of Heplisav to the following: (1) activation of plasmacytoid dendritic cells (pDCs) through TLR9 receptor recognition of the unmethylated CpG sequence, (2) conversion of pDCs into dendritic cells that present the processed HBsAg component of Heplisav to CD4+ T cells, and (3) promotion of Th1 T-cell differentiation through the production of IFN-α and IL-12. The Applicant asserts that this activation results in an enhanced and sustained antibody response to HBsAg, likely due to generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory cells.

Pharmacology: Pharmacokinetics of phosphorothioate ODNs are similar across the molecular class. Phosphorothioate ODNs are synthetic molecules in which the natural phosophodiester bonds of DNA are replaced by synthetic thioether linkages to increase stability and slow metabolism. Following intravenous or subcutaneous administration, phosphorothioate ODNs are rapidly absorbed and detected in the plasma. They bind nonspecifically and reversibly to plasma proteins. Distribution from the plasma into tissues is rapid. Based upon observations in rodents and primates, phosphorothioate ODNs primarily distribute into kidney, liver, lymph nodes, spleen, adipose tissue and bone marrow. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow (measured in days to weeks) because the phosphorothioate backbone resists degradation. Small metabolites are filtered through the glomerulus and excreted in the urine. Phosphorothioate ODNs have minimal distribution to heart, lung, and skeletal muscle and do not cross the blood-brain barrier.[1, 2, 3]

[1] Geary RS, et. al. Pharmacokinetics of a tumor necrosis factor-alpha phosphorothioate 2'-O-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos, 2003; 31(11): 1419-1428.
[2] Noll BO, et. al. Biodistribution and metabolism of immunostimulatory oligodeoxynucleotide CPG 7909 in mouse and rat tissues following subcutaneous administration. Biochem Pharmacol, 2005; 69(6): 981-991.
[3] Geary RS. Antisense oligonucleotide pharmacokinetics and metabolism. Expert Opin Drug Metab Toxicol, 2009; 5(4): 381-391.

Pre-clinical Trials

Preclinical studies of 1018 ISS alone and of the antigen and adjuvant combination were conducted. The main treatment-related findings of repeat dose toxicity studies of 1018 ISS alone in mice, rats, and cynomolgus monkeys were non-degenerative and reversible inflammatory changes at the injection-sites and in key target organs, consistent with the immunostimulatory activity of 1018 ISS adjuvant and its adjuvant class effects. Cardiomyopathy was observed in rats at a similar incidence between treatment and control groups and, given this established background finding in this animal, was assessed as not related to test article. A repeat dose toxicity study of Heplisav was conducted in mice. Epicardial mineralization was observed microscopically in animals receiving antigen with high dose adjuvant (acute phase: 50%, recovery phase: 30%) and in animals receiving the antigen alone (acute phase: 15%, recovery phase: 20%). Animals in the control group, antigen/low-dose adjuvant and antigen/mid-dose adjuvant did not show epicardial mineralization. Since epicardial mineralization is a common spontaneous lesion in mice, this finding was not determined to be treatment related. No significant toxicity was observed in the pre-clinical studies and all effects were thought to reflect the expected immunostimulatory properties of the vaccine.

Clinical Trials in the original BLA submission

Data from two multi-center, randomized, controlled, Phase 3 trials were included in the initial BLA submission: DV2-HBV-10, conducted in Canada and Germany, and HBV-16, conducted in the US and Canada. These studies compared the safety and immunogenicity of Heplisav, administered Weeks 0 and 4 (placebo administered Week 24) to that of the active comparator, Engerix-B. Engerix-B is a licensed vaccine against hepatitis B comprised of recombinant antigen adsorbed to aluminum hydroxide and administered at Week 0, 4, and 24. The Phase 3 trials were conducted in healthy subjects, age 11 through 55 years in DV2-HBV-10 and age 40 through 70 years in DV2-HBV-16. A total of 4,864 adult subjects (Heplisav: N=3,778, Engerix-B: N=1,086) were enrolled and vaccinated in the pivotal studies. Subjects were followed for AEs for 28 weeks (from first injection) in both studies, for serious adverse events (SAEs) for 28 weeks in DV2-HBV-10, and for SAEs, adverse events of special interest, and potential autoimmune events for 52 weeks in DV2-HBV-16. Additionally, there were seven other supportive trials conducted in a total of 965 subjects (Heplisav: N=632, Engerix-B: N=333) followed for safety events for various time periods. The safety database of these nine trials included 5,829 subjects (Heplisav: N=4,410, Engerix-B: N=1,419). The results of the safety evaluation of these studies performed for the first BLA review are briefly summarized here.

The overall incidence of non-serious adverse events was similar between treatment groups (Heplisav 58.1%, Engerix-B 61.2%). Solicited adverse events of fever, malaise, headache, fatigue, injection site swelling, and injection site pain occurred with similar incidence between treatment groups. More subjects receiving Heplisav reported redness at the injection site (3.5% vs. 1.0%) than did subjects receiving Engerix-B. Non-fatal SAEs were reported by 2.7% of Heplisav and 3.7% of Engerix-B recipients. Two subjects who received Heplisav and reported no history of autoimmune disease had diagnosed or suspected rare immune-mediated events following vaccination.

Two deaths occurred in study DV2-HBV-16. One 64-year-old male Engerix-B recipient (92-638) with hypertension died of cardiac arrest after having a myocardial infarction (b) (6) days after the second study injection (preferred term "cardiac failure"). One 46-year-old previously healthy male Heplisav recipient (22-003) died of a pulmonary embolus (b) (6) days after the second study injection. In the total safety database, at the time of the initial BLA submission, there was a numerical imbalance between the incidence of pulmonary embolus in Heplisav and Engerix-B recipients at 5 (0.1%) and 0, respectively, including the fatal event. Four of the five events occurred in individuals with an underlying predisposition to thrombosis; there was no noted predisposition in the subject with the fatal pulmonary embolism. SAEs of deep vein thrombosis and non-serious thrombotic events occurred with similar

incidence between groups. Three additional subjects had non-fatal myocardial infarctions reported in DV2-HBV-16, two who received Heplisav and one who received Engerix-B. In DV2-HBV-10, no deaths, myocardial infarctions, or events of stroke were reported during the 28-week study period. Table 1 presents a summary of the major cardiovascular events identified in studies of Heplisav submitted in the initial BLA. In addition to the events of AMI identified in Study DV2-HBV-16, there were two events, one in each treatment group, of myocardial infarction that were identified in the supportive studies DV2-HBV-04 and -05. Both studies were double-blind, randomized trials conducted in Asia that enrolled adults 40 – 70 years of age, randomized 1:1 to receive an earlier formulation of Heplisav (same dose of antigen and adjuvant) at Weeks 0, 8, and 24 or Engerix-B at Weeks 0, 4, and 24. In both studies, SAEs were collected through Week 50.

Table 1. Summary of cardiac deaths and myocardial infarction reported in Heplisav studies in the initial BLA submission, Safety Populations, DV2-HBV-0001, -02, -03, -04, -05, -08, -10, -14, and -16

Study	Subject #	Age	Sex	MedDRA Preferred Term	Study Day	Last Active Dose	Day of event relative to most recent active dose*
Heplisav							
DV2-HBV-16	22-003	45	M	Pulmonary embolism†	75	2	(b) (6)
DV2-HBV-16	41-335	58	M	Acute myocardial infarction	22	1	22
DV2-HBV-16	20-610	63	F	Acute myocardial infarction	44	2	15
DV2-HBV-05§	010	52	M	Acute myocardial infarction	275	3	121
Engerix-B							
DV2-HBV-16	92-638	64	M	Cardiac failure†‡	73	2	(b) (6)
DV2-HBV-16	29-614	60	M	Acute myocardial infarction and Unstable angina	39	2	11
DV2-HBV-04§	11-009	43	F	Unstable angina	182	3	14

Source: Reviewer generated summary based upon 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety (Attachment 5, and 125428/0.42, Module 5.3.5.3, dataset ADAE for the integrated studies
* Day 1 is day of administration. An event start day relative to the most recent dose of x is x-1 days following the most recent dose.
§ Study utilized a previous formulation of Heplisav
† Fatal event
‡ Following a myocardial infarction

In response to 2012 VRBPAC recommendations, the Applicant conducted randomized safety study DV2-HBV-23 in 8,300 subjects, comparing Heplisav (5500 subjects) to Engerix-B (2750 subjects). The results of this study were submitted to the BLA March 16, 2016. The Applicant submitted additional analyses regarding the imbalance in AMI via several submissions to the BLA from September 26, 2016 – October 11, 2016. CBER issued a 2nd complete response letter on November 10, 2016. The Applicant responded to the CR on Feb. 8, 2017.

Study DV2-HBV-23

This study was a Phase 3, randomized , active- controlled, observer-blinded[4] trial comparing the safety and immunogenicity of Heplisav (Weeks 0 and 4, placebo Week 24) to that of the active comparator, Engerix-B (Weeks 0, 4, and 24). Eligible subjects were randomized 2:1 to receive Heplisav or Engerix-B (approximately 5500 Heplisav and 2750 Engerix-B subjects). The Heplisav group received a 2-dose series of heplisav at 0 and 4 weeks, and placebo at 24 weeks. The Engerix-B group received a 3-dose series of Engerix-B at 0. 4 and 24 weeks. At least 413 subjects with type 2 diabetes were to be enrolled;

[4] Study subjects and personnel conducting safety evaluations were blinded to treatment assignment. Designated study personnel with no other study responsibilities were unblinded so that they could prepare and/or administer injections. An unblinded study monitor with no other responsibilities confirmed drug accountability.

enrollment was stratified by site, age group and type 2 diabetes. ECG collection was not a routine part of this trial and not all subjects underwent cholesterol/LDL collection.

The primary endpoints were as follows:

• Proportion of subjects with new-onset MAEs

• Proportion of subjects with new-onset SAEs or deaths

• Proportion of subjects with new-onset AESIs

• Proportion of subjects with new-onset AESIs + AIAEs

• SPR at Week 28 in subjects with type 2 diabetes mellitus

The study sample of 5000 (Heplisav) was powered to rule out greater than 0.49% of new-onset autoimmune disorders (or 15 new-onset cases in the Heplisav group), with a type I error of 5%.

The study included a Safety Evaluation and Adjudication Committee (expertise in autoimmune disease, infectious disease and statistics) who performed 3 pre-specified reviews and convened an addition ad-hoc meeting, at the sponsor's request, to review the cardiac deaths that occurred early in the trial; the DSMB recommended that all fatal reports and cardiac SAEs were to be submitted on a regular basis throughout the trial.

The study design attempted to minimize bias due to the large size, multiple centers (40), randomization via centralized interactive voice and web response system and blinding of the observer. The study also attempted to simulate the "real world" and limited enrollment exclusions, allowing enrollment of subjects with multiple comorbidities.

Subjects were 18-70 years of age, with no history or serologic evidence of infection with or vaccination for hepatitis B and no history of autoimmune disease. The trial enrolled 8,368 subjects (Heplisav: N=5,587, Engerix-B: N=2,781). Subjects were followed for medically attended events (MAEs), potential autoimmune events, adverse events of special interest, and serious adverse events for 56 weeks (both groups) following the first dose of study vaccine (52 weeks following the final dose of Heplisav, 32 weeks following the final dose of Engerix-B.

Subjects enrolled and vaccinated in DV2-HBV-23 had a mean age of 50.4 years (range 18-71 years) and were 50.6% male; 71.4% White, and 25.8% Black; and 90.9% not Hispanic. Overall, SAEs were reported in 345 Heplisav subjects (6.2%) and 148 Engerix-B subjects (5.3%). Non-fatal SAEs were reported in 325 Heplisav subjects (5.8%) and 142 Engerix-B subjects (5.1%). MAEs were reported in approximately 46% in both study groups.

Comments:

1. Compared to the other study populations (e.g., DV2-HBV-16, -10, -14, -22), there is an increased rate of hypertension, diabetes, smoking and obesity in the study population of DV2-HBV-23 and, since this population is at greater cardiac risk (with a larger sample and 56 week duration of follow up), there would reasonably be a higher likelihood of cardiac events in DV-HBV-23.
2. The two groups in HBV-23 appear reasonably balanced with respect to baseline cardiac risk factors, as expected in a large, randomized trial. It is not clear whether the small differences in the rate of obesity or hypertension account for the imbalance in MI.

The median age in HBV-23 and HBV-16 is higher than that reported in HBV-10, 14 and 22.

Table 2. Demographic characteristics, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, and -22)

Demographic characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16 Heplisav N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-10, -14, and -22* Heplisav N = 2042 n (%)	DV2-HBV-10, -14, and -22* Engerix-B N = 605 n (%)
Age: Mean (SD)	50.36 (11.74)	50.37 (11.68)	54.03 (7.89)	53.83 (7.81)	40.40 (9.45)	39.86 (9.01)
Age: Median	52	52	53	54	42	41
Age: Range	18 – 71	18 – 70	40 – 70	40 – 70	18 – 69	18 – 55
Sex: Male	2844 (50.9)	1391 (50.0)	943 (47.9)	236 (49.1)	938 (45.9)	261 (43.1)
Sex: Female	2743 (49.1)	1390 (50.0)	1025 (52.1)	245 (50.9)	1104 (54.1)	344 (56.9)
Race: White	3968 (71.0)	2007 (72.2)	1619 (82.3)	399 (83.0)	1868 (91.5)	555 (91.7)
Race: Black	1461 (26.1)	696 (25.0)	297 (15.1)	69 (14.3)	55 (2.7)	20 (3.3)
Ethnicity: Not Hispanic	5062 (90.6)	2541 (91.4)	1849 (94.0)	448 (93.1)	1990 (97.5)	581 (96.0)
Ethnicity: Hispanic	521 (9.3)	239 (8.6)	117 (5.9)	33 (6.9)	52 (2.5)	24 (4.0)

Source: Adapted from 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 10-5, p.60, Clinical Study Report DV2-HBV-16, Table 14.1.2-3, and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 dataset ADSL of integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group
n number of subjects reporting medical history item or characteristic
SD standard deviation
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 dataset ADSL of integrated studies

Table 3. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, and -22)

Condition or characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16* Heplisav N=1968 n (%)	DV2-HBV-16* Engerix-B N=481 n (%)	DV2-HBV-10, -14, and -22* Heplisav N = 2042 n (%)	DV2-HBV-10, -14, and -22* Engerix-B N = 605 n (%)
At least one baseline medical diagnosis of cardiac ischemia†	211 (3.8)	99 (3.6)	50 (2.5)	15 (3.1)	13 (0.6%)	2 (0.3%)
Type 2 Diabetes‡	762 (13.6)	381 (13.7)	158 (8.0)	33 (6.9)	48 (2.4)	11 (1.8)
Hypertension§	2021 (36.2)	978 (35.2)	579 (29.4)	143 (29.7)	239 (11.7)	57 (9.4)
Hyperlipidemia¶	1757 (31.4)	879 (31.6)	587 (29.8)	152 (31.6)	181 (8.9)	47 (7.8)
Sex and Age: Male ≥ 46 years	1879 (33.6)	919 (33.0)	776 (39.4)	195 (40.5)	330 (16.2)	76 (12.6)
Sex and Age: Female ≥ 56 years	1028 (18.4)	537 (19.3)	451 (22.9)	92 (19.1)	8 (0.4)	0
Smoking within 1 year	1843 (33.0)	909 (32.7)	431 (21.9)	118 (24.5)	703 (34.4)	224 (37.0)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)	863 (43.9)	205 (42.6)	542 (26.5)	167 (27.6)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86 and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of the integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group

n number of subjects reporting medical history item or characteristic
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of integrated studies
† Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease
‡ Defined as, in DV2-HBV-23, subjects identified as diabetic in the Diabetes History case report form; in DV2-HBV-16 and -10, subjects with a medical history term of diabetes and taking a drug with a WHO Drug ATC2 code of "DRUGS USED IN DIABETES"; in DV2-HBV-14 and -22, subjects with a medical history term of diabetes
§ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
¶ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow

DV2-HB-23 Deaths: There were 32 deaths in the Heplisav group (0.45%) and 7 in the Engerix-B group (0.25%), a risk difference of 200/100,000. If one excludes deaths due to illicit drug overdose or injury, there is an imbalance of 16 Heplisav subjects (0.29%) and 4 Engerix-B subjects (0.14%), or 150/100,000. If one includes only known cardiac deaths or deaths due to unknown causes, the imbalance is 10 Heplisav subjects (10/5587=0.0018 or 180 cases per 100,000) vs. 3 Engerix-B subjects (3/2781 = 0.00107, or 1.1 cases per 1000 or 108 cases per 100,000), or a risk difference of 72 cases per 100,000.

Table 4. Fatal adverse events by treatment and system organ class, Safety Population, DV2-HBV-23

Subject #	Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
Heplisav						
Cardiac						
130084	50	M	Acute coronary syndrome*	1	7	(b) (6)
131091	69	M	Acute myocardial infarction*	2	57	
112311	57	M	Hypertensive heart disease	2	63	
132082	62	M	Hypertensive heart disease*	2	212	
138012	58	F	Hypertensive heart disease	2	225	
133120	70	F	Cardiac arrest	2	243	
122613	47	M	Myocardial infarction	2	287	
104152	55	F	Cardio-respiratory arrest	2	298	
General						
119318	61	F	Death – Unknown cause	2	59	
119290	51	F	Death – Unknown cause	2	354	
Hepatobiliary						
107176	68	M	Hepatic cirrhosis	2	27	
Infectious						
106407	56	M	Hepatitis C	2	35	
Injury and Poisoning or Social circumstances						
120406	58	F	Victim of homicide†	1	1	
122628	49	M	Toxicity to various agents†	2	3	
101017	38	M	Toxicity to various agents†	2	36	
123071	62	M	Overdose†	2	88	
138246	44	M	Toxicity to various agents†	2	159	
122188	49	M	Toxicity to various agents†	2	160	
119153	42	F	Gunshot wound†	2	283	
138160	49	M	Accident†	2	286	
Neoplasm						
125113	49	M	Lung cancer metastatic	2	244	
125139	43	F	Small cell lung cancer metastatic	2	300	
Nervous system						
125045	46	F	Hypoxic-ischemic encephalopathy†	2	191	

Subject #	Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)
Respiratory						
131049	67	M	Acute respiratory failure	2	15‡	(b) (6)
121090	61	M	Acute respiratory distress syndrome§	2	120	
Engerix-B						
Cardiac						
135070	52	M	Myocardial infarction	1	12	
119175	48	M	Hypertensive heart disease§	3	27	
130392	69	M	Cardio-respiratory arrest	3	88	
Injury and Poisoning						
130269	44	M	Craniocerebral injury†	1	17	
122769	55	M	Toxicity to various agents†	2	99	
117008	33	F	Head injury†	3	162	
Neoplasm						
130252	67	M	Pancreatic carcinoma metastatic	3	179	

Source: Adapted from STN 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 12-3, p. 96
* Subject found dead. No autopsy performed.
† Events clearly due to overdose or injury.
‡ Initial event of COPD exacerbation leading to hospitalization and tracheostomy, which led to pneumonia and acute respiratory failure, began six days following Dose 2.

Table 5. Number and proportion of subjects with treatment-emergent serious adverse events in the system organ class of cardiac disorders by treatment group, Safety Population, DV2-HBV-23

MedDRA Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	14 (0.25)	1 (0.04)
Angina pectoris	2 (0.04)	1 (0.04)
Angina unstable	1 (0.02)	0
Atrial fibrillation	6 (0.11)	3 (0.11)
Atrial flutter	2 (0.04)	1 (0.04)
Bradycardia	2 (0.04)	0
Cardiac arrest	3 (0.05)	0
Cardiac failure	4 (0.04)	0
Cardiac failure acute	1 (0.02)	0
Cardiac failure congestive	9 (0.11)	3 (0.11)
Cardiac ventricular thrombosis	1 (0.02)	1 (0.04)
Cardiogenic shock	1 (0.02)	0
Cardiomyopathy	0	1 (0.04)
Cardio-respiratory arrest	1 (0.02)	1 (0.04)
Coronary artery disease	6 (0.11)	2 (0.07)
Coronary artery occlusion	1 (0.02)	1 (0.04)
Coronary artery stenosis	2 (0.04)	0
Hypertensive heart disease	4 (0.07)	1 (0.04)
Myocardial infarction	2 (0.04)	1 (0.04)
Myocardial ischemia	1 (0.02)	0
Pulseless electrical activity	1 (0.02)	0
Supraventricular tachycardia	1 (0.02)	0
Ventricular fibrillation	1 (0.02)	0
Ventricular tachycardia	2 (0.04)	0
Total Subjects with at least 1 Cardiac SAE	**51 (0.91)**	**15 (0.54)**

Source: Adapted from 125428/0.42, Module 5.3.5.1, Clinical Study Report DV2-HBV-23, Table 12-16, p. 105.
N number of subjects in each treatment group
n number of subjects reporting event
Shaded rows are events in the MedDRA standard medical query narrow for myocardial infarction.

Applicant's analyses:

1. Acute myocardial infarction MedDRA Standardized Medical Query:

In order to identify other events of myocardial infarction that may have been reported without the preferred term of AMI, the Applicant has used the Medical Dictionary for Regulatory Activity (MedDRA) standard medical query (SMQ) for myocardial infarction (MI). Preferred terms selected to identify MACE were identified in a blinded manner by Darren McGwire, MD (University of Texas Southwestern). SAEs with a preferred term in this SMQ are shaded in Table 5. Nineteen subjects in the Heplisav group (0.34%) and three subjects in the Engerix-B group (0.11%) reported an SAE with one of the five preferred terms (PTs) identified in this search. According to the applicant, the imbalance between groups was solely due to an observation in 1 preferred term (Acute Myocardial Infarction) in 1 study (HBV-23).

2. A multivariate logistic regression model evaluating factors that may be associated with myocardial infarction found only hypertension (OR = 3.78; 95% CI 1.44, 9.91) and age (OR= 1.07 for 1 year increase; 95% CI: 1.02, 1.13) were significant independent predictors of myocardial infarction. Heplisav compared with Engerix B was not a statistically significant independent predictor of events identified by the MI SMQ (OR=2.21; 95% CI: 0.76, 6.45). In this model, events identified by the MI SMQ were the dependent variable and age, sex, race, hypertension, BMI, diabetes mellitus, smoking, history of MI or stroke, and treatment group were independent variables. *(Reviewer comment: While not found via this model to be significant independent predictors of MI, smoking and diabetes are known cardiac risk factors).*

3. Major Adverse Cardiovascular Events (MACE): A composite endpoint (cardiovascular death, non-fatal MI, non-fatal stroke) and each individual component were analyzed. MACE outcomes were confirmed by post-hoc blinded central adjudication by C5Research, the academic research organization of the Cleveland Clinic. Such events were categorized as: 1) MACE event; 2) Not a MACE event; 3) Insufficient information to make a determination.

    a. Of 16 potential cardiovascular deaths (12 Heplisav, 4 Engerix-B), a total of 6 events (4 Heplisav, 2 Engerix-B) were adjudicated as contributing to the MACE outcome. Acute respiratory failure and Cardio-respiratory arrest were considered not to be MACE events. *Reviewer comments: It is not clear why "cardio-respiratory arrest" was adjudicated as a non-cardiovascular death. Other adjudication processes might have included cardiac arrest (or unknown death) as a cardiovascular death, unless there was a clear alternate explanation. See Hicks et. al. Standardized definitions paper.*
    b. Of 22 potential MI events (19 Heplisav, 3 Engerix-B),a total of 18 (16 Heplisav, 2 Engerix-B) met Cleveland Clinic criteria for MI and were adjudicated as contributing to the MACE outcome.
    c. Of 16 potential stroke events (11 Heplisav, 5 Engerix-B), a total of 15 events were adjudicated as stroke (1 Engerix-B subject with a normal brain MRI was excluded).

Reviewer Comment: The adjudicated and confirmed MACE components in study HBV-23 trend in the same direction (e.g., RR > 1.0) but the differences between the two treatments are not statistically significant for MACE or any component. There were few events that were adjudicated and confirmed as cardiovascular deaths and the adverse trend is not robust; when pooled with study HBV-16, adding one event for each treatment group, the relative risk for cardiovascular death is < 1.0, trending favorably for Heplisav.

Table 3-3: Adjudicated and Confirmed Treatment-Emergent, Serious 3-point Major Adverse Cardiovascular Events by Treatment Group (Primary Safety Population)

	HBV-16			HBV-23			PSP		
	HEPLISAV (N = 1968) % (n)	Engerix-B (N = 481) % (n)	Relative Risk (95% CI)	HEPLISAV (N = 6587) % (n)	Engerix-B (N = 2781) % (n)	Relative Risk (95% CI)	HEPLISAV (N = 9365) % (n)	Engerix-B (N = 3867) % (n)	Relative Risk (95% CI)
Composite 3-point MACE events	0.15% (3)	0.42% (2)	0.37 (0.06, 2.19)	0.50% (28)	0.22% (6)	2.32 (0.96, 5.60)	0.33% (31)	0.21% (8)	1.60 (0.74, 3.48)
Death from cardiovascular cause[a]	0.05% (1)	0.21% (1)	0.24 (0.02, 3.9)	0.05% (3)	0.04% (1)	1.49 (0.16, 14.35)	0.04% (4)	0.05% (2)	0.83 (0.15, 4.51)
Myocardial infarction[b]	0.10% (2)	0.21% (1)	0.49 (0.04, 5.38)	0.25% (14)	0.04% (1)	6.97 (0.92, 52.97)	0.17% (16)	0.05% (2)	3.30 (0.76, 14.36)
Stroke[c]	0	0	n/a	0.20% (11)	0.14% (4)	1.37 (0.44, 4.30)	0.12% (11)	0.10% (4)	1.14 (0.36, 3.56)

Source: Post hoc Tables 30.4.4, 30.4.5, 30.4.6, and 30.4.7; Post hoc Listing 7.2.
CI = confidence interval, MACE = Major Adverse Cardiovascular Events. Composite 3-point MACE comprises death from cardiovascular cause, non-fatal myocardial infarction, and non-fatal stroke; n/a = not applicable

[a] Cardiovascular cause of death comprises the following preferred terms: Death from cardiovascular cause includes death due to Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.

[b] Myocardial infarction includes deaths due to myocardial infarction and comprises the following preferred terms: Myocardial infarction includes Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, or Silent Myocardial Infarction.

[c] Stroke includes deaths due to stroke and comprises the following preferred terms: Stroke includes Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Haemorrhagic Stroke, Haemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischaemic Cerebral infarction, Ischaemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke.

NOTE: There were no deaths adjudicated as caused by myocardial infarction or stroke. There were no MACE events in HBV-10.

4. Comparison of observed vs. expected events: Observed and expected rates and numbers of adjudicated MACE events were compared. . Expected rates and numbers were estimated by applying person-years of follow up by age group, sex, and race for 35- to 70-year old whites and blacks in HBV-16 and HBV-23 to population-based data in the United States for each MACE component: 1) cardiovascular death (US Vital Statistics data from the US Centers for Disease Control and Prevention); 2) myocardial infarction (Mozaffarian, Benjamin, et al. 2015); and 3) stroke (Mozaffarian, Benjamin, et al. 2015). Expected numbers of events were also estimated using risk prediction models based on baseline cardiovascular risk factors.
   The results of the subjects identified as reporting an adjudicated MACE event in the three pivotal trials are presented in Table 9 (see also Attachment 4, p. 16). Expected rates of events were based on population-based rates of disease and two risk-prediction models (Pooled Cohort Equations and Framingham Risk Equations). In the composite MACE analysis, component MI observed in the HBV-23 Heplisav group were similar to expected (14 vs. 13) while the number in the Engerix-B group was lower than expected (1 vs. 6). The applicant concludes that the primary reason for the observed imbalance in MI in study HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group.

Table 3-4: Comparison of Observed With Expected Rates and Numbers of Major Adverse Cardiovascular Events in 35 to 70 Year-old Whites and Blacks in HBV-16 and HBV-23 (HBV-16 and HBV-23 Safety Populations)

	HBV-16		HBV-23		Pooled HBV-16 and HBV-23	
	HEPLISAV (N = 1830 person years)	Engerix-B (N = 461 person years)	HEPLISAV (N = 4893 person years)	Engerix-B (N = 2463 person years)	HEPLISAV (N = 6723 person years)	Engerix-B (N = 2904 person years)
Expected rate of MACE events	6.1/1000 p-y		6.7/1000 p-y		6.5/1000 p-y	
Expected composite MACE events -- n	11	3	33	16	44	19
Observed composite MACE events n (rate/1000 p-y)	3 (1.6)	2 (4.4)	28 (5.7)	6 (2.4)	31 (4.6)	8 (2.8)
Expected rate of cardiovascular deaths	1.5/1000 p-y		1.6/1000 p-y		1.6/1000 p-y	
Expected cardiovascular deaths -- n	3	1	8	4	11	5
Observed cardiovascular deaths n (rate/1000 p-y)	1 (0.5)	1 (2.2)	3 (0.6)	1 (0.4)	4 (0.6)	2 (0.7)
Expected rate of myocardial infarction	2.5/1000 p-y		2.7/1000 p-y		2.6/1000 p-y	
Expected myocardial infarctions -- n	5	1	13	6	18	8
Observed myocardial infarctions n (rate/1000 p-y)	2 (1.1)	1 (2.2)	14 (2.9)	1 (0.4)	16 (2.4)	2 (0.7)
Expected rate of stroke	2.1/1000 p-y		2.4/1000 p-y		2.3/1000 p-y	
Expected strokes -- n	4	1	12	6	15	7
Observed strokes n (rate/1000 p-y)	0	0	11 (2.2)	4 (1.6)	11 (1.6)	4 (1.4)

Source: Post hoc Table 80, Appendix B
MACE = Major Adverse Cardiovascular Events; p-y = person-year.
NOTE: All MACE events occurred in white and black subjects. There were no MACE events in HBV-16.

The percentage of subjects with a diagnosis of hypertension, diabetes, obesity and tobacco appears to be higher than the rates reported in Mozaffian et. al.

Table 3-5: Risk Factors for Cardiovascular Disease in the United States and in HBV-16 and HBV-23 (Safety Population)

	United States %	HBV-16 %	HBV-23 %	HBV-16 and HBV-23 %
Hypertension	32.6	29.5	35.8	34.4
Diabetes mellitus	8.5	7.8*	13.7*	12.3*
Obese	35.2	43.6	47.9	46.9
Smoker	17.9	22.4	32.9	30.5

Source: (Mozaffarian, Benjamin et al. 2015) for United States data. Post hoc Tables 51, 51.1, and 63.
* Defined as diagnosis of diabetes and taking medication for diabetes.

Table 3-6: Comparison of Observed and Expected Number of Major Adverse Cardiovascular Events and Myocardial Infarctions in White and Black Subjects and All Races Using Risk Prediction Models (HBV-16 and HBV-23 Safety Populations)

	White and Black Subjects				All Races			
	HEPLISAV		Engerix-B		HEPLISAV		Engerix-B	
Pooled Cohort Equations—ASCVD (MACE)	Observed n / N	Expected n (95% CI)	Observed n / N	Expected n (95% CI)	Observed n / N	Expected n (95% CI)	Observed n / N	Expected n (95% CI)
HBV-16	3/1916	10.9 (9.9, 11.9)	2/468	2.8 (2.5, 3.0)	3/1968	11.2 (10.1, 12.2)	2/481	2.8 (2.6, 3.1)
HBV-23	28/5429	38.6 (34.6, 42.6)	6/2703	18.5 (16.6, 20.5)	28/5587	39.3 (35.3, 43.4)	6/2781	18.9 (17.0, 20.9)
HBV-16 and HBV-23	31/7345	49.5 (44.5, 54.5)	8/3171	21.3 (19.1, 23.5)	31/7555	50.5 (45.4, 55.6)	8/3262	21.8 (19.5, 24.0)
Risk Equation for Hard CHD Framingham Heart Study								
HBV-16 *	2/1916	7.7 (6.5, 8.9)	1/468	2.0 (1.7, 2.3)	2/1968	7.9 (6.7, 9.1)	1/481	2.1 (1.8, 2.4)
HBV-23*	14/5429	24.0 (20.4, 27.7)	1/2703	11.6 9.8, 13.4)	14/5587	24.6 20.9, 28.3)	1/2781	11.9 (10.1, 13.7)
HBV-16 and HBV-23 *	16/7345	31.7 (27.0, 36.5)	2/3171	13.6 (11.5, 15.7)	16/7555	32.5 (27.6, 37.4)	2/3262	13.9 (11.8, 16.0)

Source: Post hoc Tables 62.1, 62.2, 62.3, 68.1.3, 68.1.4, 68.1.5, 68.2.3, 68.2.4, and 68.2.5.
ASCVD = atherosclerotic cardiovascular disease; Hard CHD = hard coronary heart disease; CI = Confidence Interval; MACE = Major Adverse Cardiovascular Events; PSP = Primary Safety Population.
* Observed number is for the myocardial infarction component of MACE
All observed MACE events occurred in white and black subjects. There are no MACE events in HBV-10.

5. Consideration of causality using the Bradford Hill criteria (temporality; strength/effect size; consistency; coherence; specificity/alternate explanations; biologic plausibility; analogy). The applicant's arguments include:
   a. Lack of temporal association, as evidenced by lack of imbalance through 42 days after the second injection
   b. Relative risks (RR) ranging from 0.24 in HBV-16 to 6.97 in HBV-23 (with RR for death 1.49 and RR for stroke 1.37). None of the comparisons reached statistical significance.
   c. Lack of coherence with results of other clinical trials
   d. All subjects with MI were at high baseline risk of such events
   e. Lack of biologic plausibility
   f. Other vaccines that stimulate TLR7 (influenza vaccines) associated with a reduction in the incidence of MACE events.

Kaplan-Meier Curves:
Based on the Kaplan-Meier curves, the imbalance in MACE events appears to occur after about 110 days following the first injection.

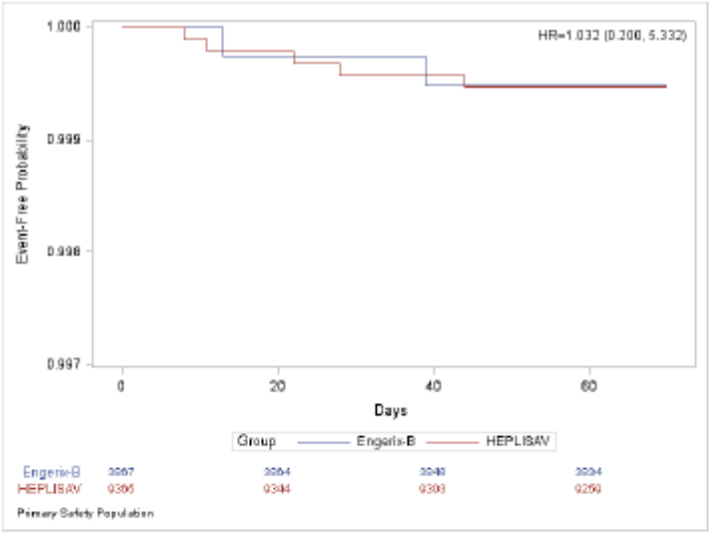

Figure 1. Kaplan-Meier curve for MACE within 70 days following first injection (source: Attachment 4, Fig. 3-1).

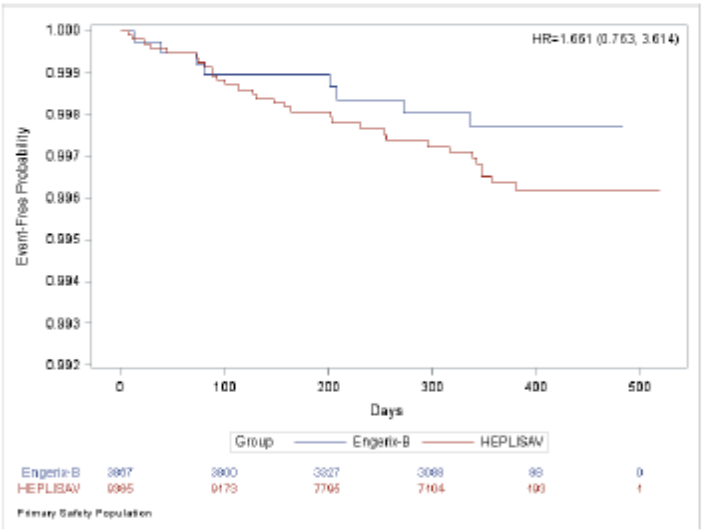

Figure 2. Kaplan-Meier Curve for MACE from first injection

Questions for the consultant

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2-HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

   Response:

- The tools listed, as well as the applicant's analysis of absolute risk and risk difference, seem reasonable in evaluating cardiac risk.

- In general, comparing rates of observed cardiovascular events in the study population to expected event rates in the overall population raises the issue of comparability. However, on its face, the sponsor's argument that MI and cardiovascular death rates in the Engerix-B group appear lower than predicted seems plausible.

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

   - In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

     Response:

     - The applicant's SMQ search for myocardial infarction seems appropriate as they included terms such as "acute coronary syndrome."

     - Since the event capture appears to have been driven by adverse events, it is possible that events (such as silent MI) were missed.

   - Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant

use the appropriate preferred terms to identify potential major adverse cardiovascular events?

Response:

- The three-point MACE analysis has been commonly used as a composite endpoint in cardiovascular outcome trials and it seems reasonable to analyze this composite outcome in a safety analysis.
- The applicant appears to have used appropriate preferred terms to identify potential MACE events.
- Depending on the underlying concern (i.e., accelerated atherosclerosis), you might consider additional analyses regarding: need for urgent revascularization, unstable angina, angina, transient ischemic attack.
- One can get to heart failure through some myocarditis syndrome without ischemic events of MI, but there is no evidence that is happening here. Heart failure can be a late consequence of MI, generally multiple MIs, but if it were related to MIs, one would expect to see the MI signal strongly first. Excluding it from the main assessment thus seems reasonable.

- In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

  Response: This question raises the issue of determining cause-specific mortality and definitions of MI, which are more difficult in the post-hoc, unblinded setting. Depending on the available data, it might be useful to you to apply the cardiovascular definitions outlined in the paper: Hicks KA et. al. Standardized definitions for cardiovascular and stroke end point events in clinical trials (available at: https://www.cdisc.org/system/files/all/reference_material/application/pdf/Draft%20Definitions%20for%20CDISC%20July%203,%202014.pdf) as a guideline. In general, we would include subjects with sudden death or unknown cause of death as cardiovascular deaths; as stated, it is unclear why cardiac arrest events were determined to be "non-cardiovascular deaths." In fact, sudden death can be a first presentation of a myocardial infarction. Our comments in this review will pertain to the available analyses.

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

   Response: The applicant's findings are consistent with the literature. According to the World Heart Federation, the leading CVD risk factors are: hypertension, followed by tobacco, elevated blood glucose, physical inactivity and obesity. While dyslipidemia is a known risk factor and can be included in the model, the risk is likely modified by factors such as LDL level and statin use.

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

   Response:

   - The three-point MACE analysis has been used as an endpoint in many previous cardiovascular outcomes studies. Such endpoints and analyses are ideally defined and conducted in a blinded, prospective manner.
   - Additional analyses can be done (e.g., MACE plus urgent revascularizations, heart failure) but their value may depend, in part, on the data collected.
   - Since the MACE events seem to depend on adverse event capture, it is possible that some events were missed or miscoded. Since HBV-23 is a large, randomized, blinded study, we would hope that any missed or miscoded events occurred at random or at a low rate and do not affect the overall results.
   - The comparison of observed to expected events has limitations, such as the comparability across populations and whether the applicant's risk model is applicable to the study population. The applicant has also acknowledged limitations of the risk models, including: 1. Conversion of the 10-year event risk to a 1-year risk under the assumption of constant risk; 2. Assumptions of cholesterol and LDL levels, since the data were not collected in all study subjects. However, even under conservative assumptions (e.g., ignoring presence of diabetes and assuming ideal lipids), the expected events still appear higher than observed in the Engerix-B group; on its face, the applicant's argument (i.e., events in the comparator group appear lower than expected) seems plausible.

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.
   Response: See above. With the limitations of cross-population comparisons and models, this argument appears plausible.

6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic

events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

Response:

- While the Hill criteria are general principles that may be useful in assessing causality, this reviewer disagrees with several conclusions made by the applicant.
    - Under "biological plausibility," the applicant advances the hypothesis that Heplisav mimics acute infection in initiating a systemic inflammatory response sufficient to trigger destabilization of a coronary plaque, and such an association would predict that events occur in close temporal proximity to an injection. We do not know that this is the case—but do not observe another biologically plausible mechanism for the observed imbalance in MI.
- You should discuss the preclinical data and safety margin of Heplisav with reviewers with expertise in animal toxicology and safety pharmacology.

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

    - There are a number of factors that make us think that this is not likely to be a reliable safety signal.
        i. An imbalance of MI that was not statistically significant was observed in study HBV-23. This imbalance was not observed in previous smaller studies; however, HBV-23 study population included a higher percentage of subjects with higher cardiovascular risk.

        ii. Analyses of adjudicated, confirmed stroke, cardiovascular death and MACE events in HBV-23 showed similar directionality (e.g., RR> 1.0), but none of the analyses showed a statistically significant difference between the two treatments. The cardiovascular death events were few and the RR was not robust.

        iii. The imbalance in cardiac events did not occur shortly after the first or second dose of vaccine; according to the Kaplan-Meier curve for MACE events, the two groups appear to separate only after 100 days. Thus, we agree with the applicant that there is not a close temporal relationship between vaccine administration and cardiovascular events. This timing is particularly incompatibile with attribution to the adjuvant.

        iv. Non-clinical and clinical studies failed to reveal a plausible mechanism for MI. The risk of MI could result from accelerated atherosclerosis, sustained increase in blood pressure, or some prothrombotic state. None of these is in evidence.

v. The sponsor's assessment that the event rate in the control arm is spuriously low is plausible. It is also plausible that the observed between-group difference is spurious.

- Based upon the low likelihood that there is a real safety signal here, and the low absolute risk that these data suggest, we would label the finding in section 6 only and consider ways to monitor this risk post-marketing through some passive surveillance system, like Sentinel.

Consultant: Thomas Wang, MD
Initital Responses
May 4, 2017

1. **Question**: In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2-HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

   Response: The Applicant has conducted an appropriate set of analyses. The most useful findings provided by the Applicant are (a) re-assessment of MACE outcomes in the phase 3 studies, and (b) the comparison of observed and expected event rates with Heplisav.

   With regard to the analysis of MACE outcomes, an independent adjudication by C5Research confirmed the numerical imbalance in cardiovascular events between Heplisav and Engerix-B, which was driven almost entirely by MI events in the HBV-23 trial. This was true despite the fact that adjudication reduced the number of cardiovascular deaths from 16 to 6, MI from 22 to 18, and stroke from 16 to 15. The relative excess in MI events was similar before (19 vs 3) and after (16 vs 2) the independent adjudication. This analysis provides some confidence that the cardiovascular findings were not the result of "overcalling" MI events. It remains possible that some MI's were missed, but it is unlikely that such misclassification would affect the arms differentially.

   The Applicant argues that MI rates in individuals randomized to Engerix-B in HBV-23 were lower than expected, which accounts for the excess risk observed in the Heplisav arm. Several analyses were performed to support this argument. First, the expected number of MI's were calculated using age- (by decade), sex-, and race-specific incidence rates generated using ARIC surveillance data and published in the AHA 2016 Statistical Update. This is the most "non-specific" of the estimates presented, as it doesn't account for risk factor differences and it is limited to the 4 communities that enroll ARIC participants.

   Next, they used the AHA/ACC Pooled Cohort Equations to estimate expected rates of hard atherosclerotic cardiovascular disease (comparable to the 3-point MACE). This

approach does incorporate information about baseline risk, although 2 variables in the Pooled Cohort Equations, total cholesterol and HDL, were not collected in HBV-23. The Applicant addressed this limitation by testing 2-scenarios: inserting predicted cholesterol and substituting "clinical optimal" cholesterol into the equation. Lastly, they used the Framingham Risk Score to estimate rates of hard coronary heart disease (myocardial infarction or coronary death) in this population. Similar assumptions were made to account for the missing cholesterol data. The AHA/ACC and Framingham models are intended only for individuals without prior cardiovascular disease, which appears to be the case for the vast majority of participants enrolled in HBV-23.

Despite the disparate comparison methodologies and endpoints, there is a consistent pattern of lower than expected coronary event rates in the Engerix-B participants in HBV-23. There is no clear explanation for this finding. It is unlikely that Engerix-B is cardioprotective, suggesting that the finding is either due to chance or to incomplete ascertainment of MI events in HBV-23. If chance is the explanation, then the apparent excess in MI risk associated with Heplisav is likely to be due to chance as well. On the other hand, if MI events were consistently under-documented in HBV-23, then the higher risk with Heplisav would still be a concern, because the missed diagnoses should be distributed among both arms. As noted above, the independent adjudication does not address this problem, because only positive diagnoses were adjudicated.

The multivariable analysis to assess risk factors for MI in the PSP sample does not provide any evidence to support the Applicant's argument. Indeed, the fact that age and hypertension were the only significant predictors of MI in their model highlights the lack of statistical power and the concern regarding incomplete ascertainment of MI events. This is because other variables in the model, such as smoking and prior MI/stroke, are known to be strong predictors of incident MI.

Lastly, the Applicant's use of the Bradford Hill criteria is only somewhat informative. As the Applicant notes, the temporal delay in the accumulation of excess MI events after Heplisav administration is difficult to explain on the basis of any known biology. On the other hand, there is still much that is not understood regarding the interaction of atherothrombotic events, inflammation, and immunity. While the Bradford Hill criteria provide a framework for organizing several lines of evidence, in my opinion the criteria cannot be used to exclude treatment-related risk.

In summary, several points raised by the Applicant in the response letter are reasonable, and the analyses are largely appropriate. That said, an important limitation of their analysis is the uncertainty regarding the completeness of ascertainment of MI events, which might explain some of the discrepancies between observed and expected risk. This limitation is inherent to the fact that HBV-23 was not designed to look at cardiovascular risk. I suspect that a broader search of terms related to myocardial infarction or ischemia (see question #2) would not yield significant additional insight regarding the numerical imbalance in MI events. There are no obvious ways to address

this limitation using the current dataset, which highlights the potential utility of collecting prospective data with regard to cardiovascular risk.

2. **Question**: Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

    a. In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

    b. Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

    c. In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

Response: The focus on terms in the myocardial infarction SMQ is reasonable, and probably favors specificity over sensitivity. Table 3-2 shows that for a subset of these terms, the clearest imbalance exists for acute MI. Many of the other terms in the SMQ for MI or ischemic heart disease are less specific and/or relate to symptoms, biochemical abnormalities, or procedural outcomes. Thus, a broader set of search terms would not necessarily provide new insight.

The 3-point MACE analysis appears appropriate. Other events such as heart failure are often not atherosclerotic in origin, so it is reasonable to omit them from the current MACE outcome. Although heart failure could be looked at separately, diagnostic criteria are more variable, and a robust analysis would require its own adjudication.

While coronary revascularization (CABG, PCI) is sometimes included in the MACE

outcome, a number of non-biological factors may influence use of revascularization. Also, with the use of contemporary troponin assays, "urgent" revascularization without biochemical evidence of necrosis is less common than in the past. Not surprisingly, the inclusion of urgent revascularization only adds 1 case per arm.

Similarly, I think it is reasonable to omit "unknown cause of death" from the cardiovascular death outcome. It has been the practice in most long-term observational studies not to assume that all unknown events are cardiovascular in origin, in part because the inclusion of unknown events does not strengthen associations with accepted cardiovascular risk factors.

3. **Question**: If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

   Response: I have concerns about the multivariable logistic regression First, there is insufficient statistical power to draw robust conclusions, given the small number of events. This is supported by the fact that known risk factors such as smoking are not significant in the model. Second, it is best to develop separate models for first and recurrent events, as the predictors are not identical. Third, the model omits covariates such as dyslipidemia. Although BMI may serve as a surrogate for dyslipidemia in primary prevention populations, this does not hold in secondary prevention populations. Lastly, for cardiovascular risk models, it is also preferable to model risk factors with continuous variables when possible (systolic blood pressure, total cholesterol, HDL cholesterol) rather than binary variables (hypertension, dyslipidemia).

4. **Question**: Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

   Response: Several concerns about the MACE analysis and comparison of observed-to-expected events are noted in the response to Comment #1. I believe that the analyses are reasonable overall based on the data available to the Applicant.

5. **Question**: Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.

   Response: It does appear that there is a consistent pattern of lower than expected event rates in the Engerix-B arm in HBV-23. Nonetheless, it is worthwhile to consider potential sources of error in the estimation of expected event rates and/or actual event rates. Challenges in estimating expected event rates include missing covariate data in HBV-23 (e.g. lipids), the mixed study sample (primary/secondary prevention), and differences in endpoint definitions between the trials and the registry/observational

datasets.

A potentially larger concern is the possibility of under-ascertainment of MI events in HBV-23, since MI was not prospectively identified as an endpoint of interest. This would explain the lower than expected events in the "control" arm (Engerix-B) and the inability of several known cardiovascular risk factors to predict MI's in HBV-23.

6. **Question**: What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

   Response: I agree with the Applicant that the temporal relation between Heplisav administration and MI events in HBV-23 does not fit a model of acute exposure causing plaque rupture. Also, the occurrence of other thrombotic events does not appear increased. These observations fit with the finding that higher doses of adjuvant exposure are required in animal models to incite an acute inflammatory response. On the other hand, it is difficult to fully exclude the possibility that lower levels of exposure could promote chronic atherosclerotic plaque formation based on animal data alone, as animal models of atherosclerosis have well-known limitations.

7. **Question**: What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

   Response: The numerical imbalance in MI events between Heplisav and Engerix-B is moderately concerning. While the finding could be attributable to chance, I cannot confidently say that there is no increased cardiovascular risk with Heplisav. Thus, I believe that further evaluation is warranted. The Applicant's analyses are a reasonable first step, but their conclusions largely hinge on the low ratio of observed to expected events with Engerix-B in the phase 3 trials. That analysis has several limitations, as described above, and it is difficult to place more weight on a comparison with externally-derived event rates (observed vs expected) than on the internal comparison (between study arms).

Stanford MEDICINE | Department of Medicine

ROBERT A. HARRINGTON, MD
ARTHUR L BLOOMFIELD PROFESSOR OF THE STANFORD UNIVERSITY SCHOOL OF MEDICINE
CHAIR OF THE DEPARTMENT OF MEDICINE

May 16, 2017

Darcie Everett, MD, MPH
Medical Officer
Food and Drug Administration
Division of Vaccines and Related Product Application
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Dr. Everett,

As requested in your April 5, 2017 e-mail, please find the responses to the consult questions.

If you have any questions or need clarification, please do not hesitate to contact me.

Questions for the consultant:

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2-HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

   Response: *In the aggregated RCT experience with Heplisav, an excess of cardiac events, notably death or myocardial infarction, was noted in the experimental treatment group compared with an active control. While none of the trials were prospectively designed to examine ischemic cardiac events, the sponsors have done an appropriate job trying to understand and place into context the observation of excess ischemic events. Unfortunately, because the question was not prospectively designed to capture this information, there was not systematic ascertainment of suspected cardiac events and the materials to support blinded (and before database unlocking) adjudication of these events. Using an adjusted analysis to understand the contribution of treatment assignment to cardiac outcomes is a reasonable approach. Focusing the post hoc adjudication exercise on a three-component composite endpoint of death, MI or stroke is reasonable and consistent with the approach taken with many contemporary randomized trials examining therapies for chronic ischemic heart disease and diabetes. Heart failure, unstable angina requiring hospitalization and revascularization procedures are often times included in various composites but the three-component composite is most frequently used and contains the most important ischemic events. The analyses that compare observed to*

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expected cardiac event rates and concludes that the active control group experienced lower than expected cardiac event rates is limited in its usefulness. Study 23 was a randomized comparison and should allow appropriate direct comparison between the treatment groups although cautions are warranted given that the endpoints were not prospectively defined nor endpoint information systematically collected. Similarly, the use of the Bradford-Hill criteria to assess causation, while interesting, has less usefulness given that the observation of excess cardiac events emerged from a randomized comparison and not from non-randomized datasets. Further insights into possible cardiac risk associated with Heplisav requires randomized comparisons and/or large post market observational studies with appropriate collection of suspected events, ECGs, biomarkers and other records needed for event adjudication.

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

   a. In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

      ***Response:** The SAEs identified are reasonable terms to seek detection of suspected myocardial infarctions. Would have been helpful to add coronary revascularization events (PCI or CABG) and heart failure as terms to increase sensitivity (while recognizing that adjudication needed for specificity).*

   b. Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

      ***Response:** The three-component composite is a reasonable one given that many/most contemporary trials in both chronic and acute ischemic heart disease use this composite in assessing efficacy of treatments. It would be reasonable to include some assessment of heart failure as an accepted measure of cardiac safety, as has been done in trials with hypoglycemic agents and NSAIDs.*

   c. In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

      ***Response:** The FDA perspective on this that includes broadening definitions and the inclusion of other terms (such as revascularization procedures) is completely reasonable as a way to increase the sensitivity around any cardiac safety signal. This approach is consistent with contemporary trials that aim to cast a broad net*

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and capture all possible related cardiac ischemic events. The sponsor, using their methodology, have chosen to increase specificity and to de-emphasize sensitivity. In an assessment of cardiac safety, an emphasis on sensitivity (broad approach to capturing possible events) is likely preferred in spirit of public health protection.

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

   Response: *Given that the trial plan did not pre-specify a formal planned comparison of ischemic cardiac events between the treatment, there are a number of limitations in the comparison, including the multiplicity issue. Multivariate logistic regression is a reasonable way to compare the treatments for ischemic cardiac risk. The variables included in the model are appropriate ones and consistent with much contemporary cardiovascular research.*

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

   Response: *As previously stated, the use of the three-component composite is quite reasonable and consistent with many contemporary cardiovascular trials. Given that the current program(s) is addressing the issue of cardiac safety (rather than efficacy), adding other components such as hospitalization for cardiac causes would be quite reasonable as well. Because Study 23 is a randomized trial and of a sufficient sample size to assure a reasonable balance between the treatment groups, the most appropriate comparison is between the vaccine therapies. The expected versus observed analyses are interesting and lend some insight into the overall event rate but should not supersede the randomized comparisons.*

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.

   Response: *Study 23 was a large RCT that looks to have appropriately balanced groups that allow a direct comparison of the treatment groups. The expected versus observed analyses are interesting but less so than the comparison based on randomization. Other observational datasets may well generate different event rates.*

6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

   Response: *The Bradford Hill criteria can be useful for providing insight into an observation and possible causation. Most often, the criteria are used in assessing the strength of evidence in epidemiological research when treatment (or exposure) comparisons do not have the benefit of being a randomized comparison. In the*

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example given in these data, one might suppose alternative biological hypotheses that would be opposite offered up by the sponsor. The reality is that the biological suppositions are hypotheses and not facts. Additionally, the mechanistic issue is not likely to be progression of atherosclerosis over such a short period of observation but rather some biological mechanism that contributes to plaque instability and/or heightened response to thrombosis.

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

   Response: *The sponsor has observed an imbalance of ischemic cardiac events (mostly myocardial infarction) associated with use of its vaccine compared with an active control vaccine in a large randomized clinical trial. The trial was not prospectively designed to optimally identify suspected ischemic events, to have appropriately collected supporting materials on these events nor to prospectively adjudicate suspected events. The trial did however enroll a group of patients at increased cardiac events based on entry cardiac risk factor profiles. The sponsor has performed a very reasonable series of analyses intended to "explain" or to minimize this infrequent, but troubling, difference in cardiac risk. The observation is consistent across several cardiac events, including unexplained death and myocardial infarction. In Study 23, the comparison of the MACE composite does not meet conventional statistical significance. The sponsor cannot/does not fully eliminate the notion that this is a "real" observation worth further investigation. I agree.*

Sincerely,

/s/

Robert Harrington, MD
Arthur L. Bloomfield Professor and Chairman
Department of Medicine, Stanford University

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